UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE S.A., et al., Plaintiffs, v. DR. REDDY'S LABORATORIES LTD., et al., Defendants.	CIVIL ACTION NO. 11-3962 (MLC) **SUPPLEMENTAL OPINION**

COOPER, District Judge

This is an action arising under the Hatch-Waxman Act, 35 U.S.C. § 271(e)(2)(A). Plaintiffs, Helsinn Healthcare S.A. ("Helsinn") and Roche Palo Alto LLC ("Roche") (collectively, "plaintiffs"), are assignees of U.S. Patents No. 7,947,724 ("the '724 patent"), No. 7,947,725 ("the '725 patent"), No. 7,960,424 ("the '424 patent"), and No. 8,598,219 ("the '219 patent"). The four patents-in-suit are listed in the FDA "Orange Book" as covering plaintiffs' product Aloxi®, which is a pharmaceutical composition containing the active ingredient palonosetron. The version of Aloxi® currently marketed by plaintiffs is an intravenous solution with approved indications for preventing or treating cancer chemotherapy-induced nausea and vomiting.

Plaintiffs brought this action, and related consolidated actions, against generic drug manufacturers, Dr. Reddy's Laboratories, Ltd., Dr. Reddy's Laboratories, Inc.

("DRL"), Sandoz, Inc. ("Sandoz"), Teva Pharmaceuticals USA, Inc., and Teva Pharmaceutical Industries, Ltd. ("Teva"). Plaintiffs alleged that each group of defendants had filed an Abbreviated New Drug Application ("ANDA") containing so called "Paragraph IV" certifications asserting that the claims of the patents-in-suit were invalid and/or not infringed. The asserted claims are claims 2 and 9 of the '724 patent, claim 2 of the '725 patent, claim 6 of the '424 patent, and claims 1, 2, 6, and 7 of the '219 patent. The pertinent limitations of the first three patents are "reducing emesis...," the "0.05 mg/mL" concentration, and "EDTA." The pertinent limitations of the '219 patent are "reduce ... cancer chemotherapy-induced nausea and vomiting," "0.25 mg" dose in "5 mL ... solution," and "EDTA."

Defendant Sandoz was dismissed from the action by consent, on December 31, 2014. (Dkt. 247.)[1] The Court issued a Memorandum Opinion construing certain preamble language in the '219 patent claims, on April 22, 2015. (Dkt. 290.) An 11-day bench trial was conducted in June 2015, with closing arguments presented on August 12, 2015. (Dkts. 320, 322, 324, 326, 328, 330, 331, 337, 340, 342, 344, and 353.) Defendant

[1] The Court will cite to the documents filed in this case in the Electronic Case Filing System ("ECF") by referring to the docket entry numbers by the designation of "dkt." References to docketed materials are to ECF pagination. The two later-filed actions that have been consolidated into this lead case are Civil Action No. 11-5579 and Civil Action No. 13-5815. Copies of the four patents-in-suit are attached as exhibits to the pleadings, and are trial exhibits. We will simply cite to the patents by page or column and line number. Those patents are trial exhibits numbered as follows: '724 patent (DTX-0069), '725 patent (DTX-0070), '424 patent (DTX-0001 and DTX-0071), and '219 patent (DTX-0268).

DRL was dismissed on stipulation on October 16, 2015. (Dkt. 355.)[2] Thus, the current parties in this case are plaintiffs and Teva.

Teva asserts that the asserted claims of each of the four patents-in-suit are invalid as obvious under 35 U.S.C. § 103.[3] Teva further asserts invalidity of those patents under the on-sale bar provision of 35 U.S.C. § 102. The on-sale bar issue presents not only underlying factual questions, but also a statutory interpretation question addressing the amended text of § 102(a)(1) under the America Invents Act ("AIA"), Pub.L. No. 112-29 (2011). Teva also raises a written description claim against those patents under 35 U.S.C. § 112. Plaintiffs oppose each of Teva's points on those issues, asserting that the patents are valid and enforceable.

There is also an infringement issue. Teva filed one consolidated ANDA, seeking approval for products at two different dose levels (0.25 mg and 0.075 mg), and two different treatment indications (chemotherapy-induced nausea and vomiting ("CINV") for the 0.25 mg dose, and post-operative nausea and vomiting ("PONV") for the 0.075 mg dose). The concentration of both proposed Teva products is 0.05 mg/ml, because the 0.25

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[2] DRL and plaintiffs have a related action, actively pending in this Court, pertaining to the '724 patent and DRL's pending 505(b)(2) New Drug Application under 21 U.S.C. § 355(b)(2). See Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al., Civil Action No. 12-2867. In that case, the Court issued a Memorandum Opinion and Order on April 2, 2015, construing the '724 claim term "a chelating agent." (Civ. Action No. 12-2867, dkt. 91 (Order) and dkt. 92 (SEALED Mem. Op.).)

[3] Teva has advised that it will not appeal the ruling of this Court that the patents-in-suit are valid under 35 U.S.C. § 103 (obviousness). This Court will issue a separate Supplemental Opinion providing further rulings on that issue as necessary.

mg dose solution is 5 ml and the 0.075 mg dose solution is 1.5 ml. The asserted '219 patent claims only specify a 0.25 mg dose, in a 5 ml volume (i.e., concentration 0.05 mg/ml), for CINV. Plaintiffs assert that if the '219 claims are held to be valid, those claims are infringed by Teva's ANDA filing itself, according to the Hatch-Waxman Act, and therefore both generic products applied for in Teva's ANDA must infringe and be enjoined. Teva disputes plaintiffs' legal position and seeks a declaration that its 0.075 mg dose PONV product will not infringe the asserted '219 patent claims.

The Court issued a Memorandum Opinion on November 13, 2015, and entered judgment declaring that:

> (1) the asserted claims of the '724, '725, and '424 patents are valid and are infringed by both Teva's proposed 0.25 mg and 0.075 mg generic products;
> (2) the asserted claims of the '219 patent are valid and are infringed by Teva's proposed 0.25 mg generic product; and
> (3) the asserted claims of the '219 patent are valid and are not infringed by Teva's proposed 0.075 mg generic product.

(Dkt. 360; dkt. 361.)

This Supplemental Opinion constitutes the Court's findings of fact and conclusions of law on the issues of the on-sale bar under 35 U.S.C. § 102, statutory interpretation of the on-sale bar after the passage of the American Invents Act under 35 U.S.C. § 102(a)(1), written description under 35 U.S.C. § 112, and infringement under 35 U.S.C. § 271. The Court now makes the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a)(1).

I. FINDINGS OF FACT

A. Medical treatment for emesis

Medical science has long recognized that the human body has an elaborate and multifaceted defense system against trauma and toxins. (Dkt. 328 at 29.) Part of that defense system is called emesis, referring generally to the reflexive reaction experienced as nausea and vomiting. (Id. at 27, 31–32.) Its purpose is essentially to get rid of toxins in the body. (Id. at 26.)

The parties presented undisputed medical background information on the scientific field of the claimed inventions. (Id.; see also dkt. 320; dkt. 324; dkt. 326; dkt. 331; dkt. 337; dkt. 340; dkt. 342; dkt. 344.) For example, Teva's expert clinician Dr. David Frame provided a basic overview of the mechanisms in the body that lead to emesis, at least as related to chemical stimuli.[4] As he explained, the gastrointestinal tract and the brain are the two primary systems involved in creating emesis. (Dkt. 328 at 25–26.) If a person ingests a toxin directly into the stomach, or if a toxin is injected into the blood, the noxious substances go into the GI tract. (Id. at 26.) The GI tract then releases certain molecules called neurotransmitters. (Id.) Those neurotransmitters will bind to receptors, causing signals to transmit up a nerve called a vagal nerve that leads to a specific spot located in the brain but just outside the blood-brain barrier (the trigger zone or essentially

[4] Dr. Frame explained that he uses the term "emesis" to refer to vomiting, as distinguished from nausea. (See dkt. 328 at 31.) Other witnesses and some of the prior art would use the term "emesis" more broadly to refer to nausea and vomiting. (See, e.g., dkt. 331 at 20.) We use the term in that broader sense, except when referring to testing results that pinpoint those aspects separately.

the vomiting center). (Id.) When those neurotransmitter signals arrive there, they will activate one or more neurotransmitters that will carry the signal back down the vagal nerve to the GI tract and produce the contractions of nausea and vomiting. (Id. at 27.)

Scientists have identified approximately 20 to 30 types of neurotransmitters that play a role in prompting the emesis reaction. (Id. at 28.) Those neurotransmitters bind to cells called receptors, found in various places in the body. (Id. at 28–29.) In other words, several different neurotransmitters and corresponding receptors are involved in most causes of nausea and vomiting. (Id. at 29.) Also, depending on what kind of toxic stimulus is introduced, there may be different amounts and types of neurotransmitters activated, and different locations within the body where the corresponding receptors are concentrated. (Id. at 28–29.) All of this is part of that elaborate defense system against various toxic substances that is inherent in the body. (Id. at 26, 29.)

One of the neurotransmitters known to play a role in causing emesis is serotonin (5-hydroxytryptamine). (Id. at 28.) It can bind to many different types of receptors, but the one that it binds to that is most responsible for nausea and vomiting is a specific "hydroxytryptophan" receptor, called the 5-HT3 receptor. (Id. at 29.) Indeed, there are different types of hydroxytryptophan receptors, and the number 3 type (the "5-HT3 receptor") is known to be specific in binding with serotonin to release those nausea and vomiting signals. (Id.)

Some of the other types of neurotransmitters known to participate in prompting emesis (with corresponding varieties of receptors) are dopamine and something called

Substance P that binds to neurokinin receptors. (Id. at 29, 33.) For this reason, among others, clinicians trying to prevent or treat emesis will often use a multifaceted approach. (Id. at 29.) Instead of relying on just one type of drug product, they will use a combination of therapies. (Id.) The pharmaceutical products used in this effort, that target various receptors and their corresponding neurotransmitters, are referred to as "antagonists." (Id. at 30.) Thus, compounds directed to serotonin and the 5-HT3 receptor are called "serotonin receptor antagonists" or "5-HT3 receptor antagonists." (Id.)

There are also timing and toxin factors in selecting "antiemetic" therapies. For example, some toxins used in medical treatment, or dosage levels of those toxins, are considered "highly emetogenic," whereas others may be considered "moderately emetogenic." (Id. at 148; dkt. 324 at 52.)

It is recognized that the onset and duration of emesis may vary, depending on the situation. (Dkt. 328 at 38.) So antiemetic therapy will look at effects in the immediate time period after introduction of a toxin, as well as in the succeeding hours and days. (Id.) Those time periods are referred to as the "acute emesis" period for the first 24 hours, and "delayed emesis" thereafter. (Id. at 38–39.) These time periods are a recognized feature of designing and studying antiemetic care.

Another defining concept in the antiemetic field is the distinction between so-called "post-operative nausea and vomiting," or PONV, and "cancer chemotherapy-induced nausea and vomiting," or CINV. (Id.) Both sorts of reactions are encompassed within the general term "emesis," but clinicians typically will select antiemetic therapies

with that distinction in mind. (Id.) For example, the claims of the '219 patent-in-suit are directed to "cancer chemotherapy-induced nausea and vomiting." See Section I.B. The claims of the other three patents-in-suit are directed more broadly to "emesis." (Id.)

Aloxi® is the brand name of plaintiffs' antiemetic product, listed in the FDA Orange Book as covered by the four patents-in-suit. The active ingredient in Aloxi® is palonosetron hydrochloride, which is a serotonin antagonist or so-called 5-HT3 antagonist. It is currently marketed in the United States in the form of an intravenous 0.25 mg dose in 5 ml solution (resulting in palonosetron concentration of 0.05 mg/ml). At that dosage, it has FDA-approved indications for preventing CINV in both moderately and highly emetogenic cancer chemotherapy, including delayed CINV with respect to the moderately emetogenic chemotherapy. (DTX-1244-0002.) A later-approved additional indication is at a one-third lower dosage of 0.075 mg for prevention of PONV, but it is not currently marketed in that form. (Id.; dkt 331 at 85.)

The compound Aloxi®, with its label information, received FDA approval on July 25, 2003, after a lengthy new drug application process. See n.39 infra. The provisional patent application to which the four patents-in-suit claim priority was filed on January 30, 2003. The parties agree that the relevant date for analyzing prior art (as well as for the on-sale bar factual issues) is January 30, 2002. See n.61 infra. As the discussion in this opinion will demonstrate, the patent validity issues in this case focus heavily upon the history of the Aloxi® drug development process in that time frame.

B. The patents-in-suit

The four patents-in-suit are each named "Liquid Pharmaceutical Formulations of Palonosetron." They are all composition patents. (Dkt. 290 at 2.) There are other patents and patent applications in the same patent family history. (Id.; dkt. 289.)

Each of the patents-in-suit claims priority to the original provisional application date, January 30, 2003, although they have different effective filing dates. (Dkt. 289.) In chronological order of issuance, they are the '724 and '725 patents, issued on May 24, 2011; the '424 patent, issued on June 14, 2011; and the '219 patent, issued on December 3, 2013. (Id.)

All four patents are subject to terminal disclaimer, and will expire no earlier than July 30, 2024. (Dkt. 361 at 3.) The parties agree that the first three patents are subject to the patent provisions in effect prior to enactment of the AIA, and the '219 patent is subject to the AIA for purposes of this case. In fact, the '219 patent was applied for and granted during the pendency of this litigation. (Dkt. 289.) This case was filed on July 8, 2011. (Dkt. 1.) The effective application date of the '219 patent was May 23, 2013, after the pertinent effective date of the AIA. (Dkt. 289.)

The asserted claims are the '724 patent, claims 2 and 9; the '725 patent, claim 2; the '424 patent, claim 6; and the '219 patent, claims 1, 2, 6, and 7. (Dkt. 174 at 2.) This Court has issued a claim construction opinion that construed the preamble language of the asserted claims to be claim limitations. (Dkt. 290.)

Claim 2 of the '724 patent is representative of the asserted claims of the '724, '725, and '424 patents. Rewritten to incorporate claim 1 of the '724 patent on which it depends, claim 2 states:

> A pharmaceutically stable intravenous solution for reducing emesis or reducing the likelihood of emesis comprising:
>
> a) about 0.05 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, buffered at a pH of from 4.0 to 6.0; and
>
> b) a pharmaceutically acceptable sterile aqueous carrier including a tonicifying effective amount of mannitol and from 0.005 mg/ml to 1.0 mg/ml EDTA.

('724 patent, col. 9, line 27, to col. 10, line 3.)

Asserted claim 1 of the '219 patent, on which asserted claims 2, 6, and 7 of that patent depend, states:

> A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising a 5 mL sterile aqueous isotonic solution, said solution comprising:
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> palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base;
>
> from 0.005 mg/mL to 1.0 mg/mL EDTA; and
>
> from 10 mg/mL to 80 mg/mL mannitol,
>
> wherein said formulation is stable at 24 months when stored at room temperature.

('219 patent, col. 10, lines 1–12.)

The written descriptions of the four patents are generally similar. For example, the specification of each patent contains the following sentence, giving the exact dosage and/or concentration appearing in the asserted claims:

> In one particular embodiment the palonosetron is supplied in vials that comprise 5 ml. of solution, which equates to about 0.25 mg of palonosetron at a concentration of about 0.05 mg/ml.

(See '724 patent, col. 4, line 66, to col. 5, line 2; '725 patent (same); '219 patent (same); '424 patent, col. 5, lines 14–17.)

C. Factual chronology

It is necessary to set forth in detail the factual history of the pharmaceutical development process that led to the patents-in-suit, and to the marketing of Aloxi® as their commercial embodiment. That factual history is undisputed, but the parties differ sharply as to the legal consequences of the facts, particularly in analyzing Teva's validity challenges based on both obviousness and the on-sale bar.

An important distinction must be borne in mind when reviewing this factual history. For purposes of the obviousness analysis, the focus must be on the state of the art as publicly known; that is, the published prior art and what a skilled artisan would have known. In fact, the actual process of invention that led to the claimed invention is considered irrelevant under obviousness analysis. See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1364 (Fed.Cir. 2008). In sharp contrast, the legal tests for the on-sale bar require a court to look also at facts that were not public; for example, to determine whether the invention was "ready for patenting" more than one year before the patent application date. See Section II.A.4.

One fact that is pivotal to both the obviousness and the on-sale bar issues is that the provisional application date for all four patents-in-suit was January 30, 2003. (See

dkt. 289.) Therefore, the date of January 30, 2002, is the critical date for purposes of the on-sale bar. See 35 U.S.C. § 102, amended by Leahy-Smith America Invents Act, Pub.L. No. 112-29, 125 Stat. 254 (2011). That same date of January 30, 2002, is also the date for obviousness analysis of the published prior art references, as stipulated by the parties. (Dkt. 328 at 240–41.)

Here we set forth both the publicly known and the behind-the-scene facts in recounting this history. In Section II the parties' arguments on their many legal issues are addressed by reference to these facts.

1. Syntex and the genus '333 patent

There was a group of scientists in Palo Alto, California, doing research in a company named Syntex (U.S.A.), Inc. ("Syntex"), beginning in the late 1980's. In May 1991, Syntex filed a patent application that resulted in issuance of U.S. Patent No. 5,202,333 ("the '333 patent") on April 13, 1993. (DTX-0343.)

The '333 patent disclosed "novel compounds which are 5-HT3 receptor antagonists," in particular, "tricyclic 5HT3 receptor antagonists containing a bridged bicyclic amine substituent." (Id., col. 1, lines 9–14.) There were three independent claims and many dependent claims. Claim 1 was to "a compound of Formula I," which was an extremely broad genus-type formula. (Id., col. 34, line 15, to col. 35, line 14.) Independent claim 40 made the following pharmaceutical composition claim:

> A pharmaceutical composition for treating a condition chosen from emesis, a gastrointestinal disorder treatable with prokinetic agents, anxiety/depressive state, and pain, which composition comprises a

> therapeutically effective amount of a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

(Id., col. 37, lines 10–17.) Independent claim 41 claimed a method for treating a condition chosen from those disorders, "in an animal in need of such treatment." (Id., col. 37, lines 18–24.)

"Emesis" was a defined term in the '333 patent, quoted here in the margin.[5] "Disease" was defined to include "the emesis caused by therapy with agents having emetogenic side effects, in particular by therapy for cancer, such as chemotherapy with cytotoxic agents...." (Id., col. 4, lines 33–41.) "Treating" was defined to include preventing, inhibiting, or relieving the "disease." (Id., col. 5, lines 33–40.)

The Background of the Invention section of the '333 specification explained serotonin and its receptors, in pertinent part as follows:

> Serotonin, a neurotransmitter with mixed and complex pharmacological characteristics, was first discovered in 1948 and subsequently has been the subject of substantial research. Serotonin, also referred to as ... (5-HT), acts ... on discrete 5-HT receptors ... [which] are presently delineated into three major subclassifications -- 5-HT1, 5-HT2 and 5-HT3.... Receptors of the 5-HT3 subclass ... appear to regulate the release of a variety of neurotransmitters in the gastrointestinal, cardiovascular and central nervous systems.
>
> 5-HT3 receptors are located in high densities on neurons associated with the emetic reflex and drugs which block the interactions of serotonin at the 5-HT3 receptor level, i.e., 5-HT3 receptor antagonists, possess potent antiemetic properties. Such antagonists demonstrate utility for counteracting the emetic effects of cancer chemotherapy and radiotherapy.

(Id., col. 1, lines 19–41.)

[5] The '333 written description stated: "'Emesis', for the purposes of this application, will have a meaning that is broader than the normal, dictionary definition and includes not only vomiting, but also nausea and retching." (DTX-0343, col. 4, lines 42–45.)

The parties agree that palonosetron is one of the myriad compounds claimed within Formula I of the '333 patent, although the exact chemical name and structure of palonosetron is not specified.[6] The number of compounds claimed in the '333 patent is not quantified in the patent itself or in any of the trial evidence, but expert testimony at trial indicated that the amount of possible combinations that could be claimed within the patent formula was "huge." (Dkt. 328 at 172.)

The '333 specification reported that the inventors had employed accepted testing methods to determine activity of "the compounds of Formula I" in animals. (DTX-0343, col. 11.) That testing included in vitro assay of rat brain tissue, as well as in vivo testing of anesthetized rats, to measure 5-HT3 "receptor binding affinity" of the compounds. (Id., col. 11, lines 5–11.) It also included in vivo measurement of "anti-emetic activity" of the compounds in reducing emesis induced by a chemotherapy agent (specifically, cisplatin) in ferrets and in dogs. (Id., col. 11, lines 11–35.)

As seen in the claim language of the '333 patent, the planned uses of its compounds were not confined to antiemetic treatment. (Id., col. 37, lines 10–26; col. 38, lines 1–7.) Other "diseases" such as gastrointestinal disorders, anxiety, and pain were also listed. (Id., col. 37, lines 18–23.) When discussing administration of the claimed compounds, the '333 specification gave correspondingly broad descriptions of possible

[6] Teva's formulator expert, Dr. Kirsch, identified this language in the '333 specification as including palonosetron: "Of most interest are the compounds of Formula I in which each p, q and u are O, and R3 is 1-azabicyclo[2.2.-2]oct-3-yl, in particular wherein one or, when present, both chiral centers possess S configurations." (Dkt. 326 at 189 (quoting DTX-0343, col. 9, lines 23–26).)

routes of administration,[7] dosing levels,[8] and drug concentration formulations,[9] as quoted in the margin. Regarding dosage, the specification also stated: "One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of a compound of Formula I for a given disease." (Id., col. 12, lines 19–24.)

The '333 patent specification provided Example 13 as "representative pharmaceutical formulations containing a compound of Formula I." (Id., col. 28, lines

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[7] The '333 specification stated: "In general, compounds of Formula I will be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous)." (DTX-0343, col. 12, lines 25–29.)

[8] The '333 specification addressed dosage of a "pharmaceutically effective amount" as follows:

> A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. Therapeutically effective amounts of compounds of Formula I may range from approximately 1.0 nanogram per Kg (ng/Kg) body weight per day to 1.0 mg/Kg body weight per day. Preferably the amount will be approximately 10 ng/Kg/day to 0.1 mg/Kg/day. Therefore, a therapeutically effective amount for a 70 Kg human may range from 70 ng/day to 70 mg/day, preferably 700 ng/day to 7.0 mg/day.

(DTX-0343, col. 12, lines 7–18.)

[9] The '333 specification discussed drug concentration as follows:

> The amount of a compound of Formula I in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, the final composition will comprise from 0.000001% w to 10.0% w of the compound of Formula I, preferably 0.00001% w to 1.0% w, with the remainder being the excipient or excipients.

(DTX-0343, col. 12, lines 60–68.)

55–56.) It included examples for an oral solution, an intravenous solution, and a tablet. The intravenous formulation in Example 13 was:

Compound of Formula I	10-100 mg
Dextrose Monohydrate	q.s. to make isotonic
Citric Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.18 mg
Water for Injection	to 1.0 ml

(Id., col. 29, lines 6–11.)

The Syntex inventors continued their research involving the compounds claimed in the '333 patent into the mid-1990's, as described next.

2. Roche Syntex further development process

Syntex pursued the development of its '333 patent compounds through several steps in its research process. That research included the laboratory studies referred to in the specification of the '333 patent, and other studies documented in its own internal "formulation books." (Dkt. 320 at 27–28.)

Syntex filed an Investigational New Drug ("IND") application, number 39,797, with the FDA on June 2, 1992. (See PTX-261.0002.) The subject of the IND was investigation of palonosetron hydrochloride, designated RS-25259-197 ("RS-25259"). (See id.)

As Helsinn later stated to the FDA, in summarizing the Syntex preclinical (animal) studies leading to that IND application, "[e]xtensive *in vitro* and *in vivo* pharmacologic studies for palonosetron have been conducted." (DTX-293-0031.) Among the key findings from those studies was that palonosetron "has a high affinity and specificity for

5-HT3 receptors," and "[p]alonosetron is effective in animal modes of chemically induced emesis by both oral and intravenous routes." (Id. at -0031 to -0032.)

The Syntex research under its IND progressed through Phase I and Phase II clinical testing of RS-25259. (See dkt. 320 at 30–32.) The Phase I clinical studies were to determine safety and pharmacokinetics of the palonosetron, by administering it as an intravenous injection to healthy human volunteers. (DTX-0293-0032.) Once the Phase I clinical studies were complete and indicated safety of the drug, Syntex obtained FDA approval and proceeded to Phase II studies, which it worked on through approximately 1995. (Id. at -0032 to -0035; dkt. 320 at 31–32.) The pharmacokinetic data from the Phase I studies also indicated that "[t]he mean plasma elimination half-life ... was approximately 40 hours in subjects given single IV or oral doses." (DTX-0293-0033.)

Generally, in a Phase II clinical study, the active pharmaceutical ingredient ("API") is administered to actual patients, to continue assessing safety but also to start determining effective dosage levels in humans. (See dkt. 320 at 31.) If Phase II studies are completed and accepted by the FDA, the applicant may request to proceed to Phase III, which is typically a large-scale study conducted with an actual pharmaceutical formulation, including excipients and packaging, involving patients in many locations. In Phase III, the safety and efficacy of the formulation is measured in the patients, and stability and manufacturing quality of the product are tested in samples. (Id.)

Syntex was acquired by the Roche pharmaceutical organization ("Roche") at some time prior to 1995. (Dkt. 320 at 127.) Syntex was then known as Roche Syntex, or officially Roche Palo Alto LLC. (See id.; '724, '725, '424, and '219 patents, page 1.)

Several Phase II clinical trials to evaluate safety and efficacy of palonosetron hydrochloride were conducted by Roche Syntex under its IND. Again as later summarized to the FDA by Helsinn, those studies were as follows:

> Study 2330: Intravenous for prevention of highly emetogenic CINV.[10]
> Study 2332: Oral for prevention of highly emetogenic CINV.
> Study 2500: Intravenous for PONV.
> Study 2502: Oral for PONV.

(See DTX-0293-0033.)

The Phase II Study 2330 ("the 2330 study") was named "A dose-ranging, efficacy, safety, and pharmacokinetic study of single intravenous doses of RS-25259 for prevention of nausea and vomiting in chemotherapy-naive cancer patients receiving highly emetogenic chemotherapy." (DTX-0227-0005.) That study started in May 1994. (See id.) The Final Report of that study was dated July 1995, and signed on September 25, 1995. (DTX-0227-0005, -0016.)

The Introduction section of the 2330 study Final Report stated in part as follows:

> Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents such as cisplatin are used. Nausea and vomiting may be triggered by the release of ... (5-HT) via a cascade of neuronal activation involving both the gastrointestinal tract and the central nervous system. Emesis may be seen acutely (within 24 hours of

[10] There was another Phase II clinical trial also directed to intravenous use in prevention of highly emetogenic CINV (Study 2120), but it was discontinued due to poor patient enrollment. (See PTX-261.0002.)

> the start of chemotherapy), after a delay (beginning 24–48 hours after chemotherapy), or even in anticipation of chemotherapy.... With repeat courses of chemotherapy, emesis becomes progressively more difficult to control, although adequate control in the first chemotherapy cycle is more likely to be associated with control of acute emesis in subsequent cycles. Therefore, antiemetic efficacy is generally studied first in chemotherapy-naive patients.
>
> In the United States, currently available antiemetic therapies include either single-drug or combination therapy with phenothiazines, steroids, or metoclopramide (a mixed 5-HT3 and dopaminergic-receptor antagonist), or most recently ondansetron (a 5-HT3 receptor antagonist). All of these therapies must be given as multiple-dose regimens because of their short half-lives, and none is completely effective in preventing the severe nausea and vomiting associated with cancer chemotherapy.
>
> RS- 25259-197 (hereafter referred to as RS-25259) is a novel, potent, and selective 5-HT3 receptor antagonist. In animal models of chemotherapy-induced emesis, RS-25259 completely inhibits emesis in up to 100% of animals given high-dose cisplatin. In humans, the mean half-life of the drug is approximately 40 hours, whether administered intravenously or orally. Given the high affinity for the receptor, excellent efficacy in animals, and long half-life in humans, a single dose of RS-25259 may control acute chemotherapy-induced emesis.
>
> This was the first randomized, double-blind trial of intravenously administered RS-25259 in chemotherapy-naive cancer patients.

(DTX-0227-0017 to -0018 (footnotes omitted).)

The stated objectives of the 2330 study included: "(1) [to] determine the dose-response relationship among single IV doses of RS-25259 over the dose range 1–90 µg/kg...." (Id. at -0014.) The Final Report of the 2330 study concluded as follows:

> RS-25259, administered as a single intravenous bolus injection of 3, 10, 30, or 90 µg/kg 30 minutes prior to high-dose cisplatin chemotherapy, was effective in suppressing chemotherapy-induced emesis for 24 hours. All four doses were approximately equally effective as compared with the combined results from a cohort of 0.3 and 1 µg/kg.

> ....
> Based on the results of this study, a dose of 3 µg/kg or 10 µg/kg RS-25259 might be appropriate for further development.

(Id. at -0015 to -0016.)

The 2330 study Final Report also noted the following pharmacokinetic observations: "The plasma half-life was exceptionally long for this class of compound, and a few patients demonstrated very long half-lives compared with the other patients." (DTX-0227-0016.)

There were, however, significant questions about effective dosage levels remaining at the end of the 2330 study, as described in that same 2330 study Final Report. The Discussion section of the Report stated as follows:

> A statistically supported dose-response relationship for efficacy ... between the lowest dose level of RS-25259 and each subsequent higher dose level was not observed in this study. The statistical analyses, defined prior to study start, were essentially confounded by the relatively high response rate observed among patients who received the lowest dose of RS-25259, namely 0.3–1 µg/kg. This was not expected and the reasons for this response are unclear. One could perhaps speculate and perform additional statistical tests, but that would be beyond the scope of the preplanned analysis.
>
> Nevertheless, based on published data that shows that almost all patients who receive high doses of cisplatin experience nausea and vomiting, the results of this study suggest that RS-25259 is an effective agent. Based on clinical observation, a single intravenous bolus injection of 3, 10, 30 and 90 µg/kg RS-25259 30 minutes prior to cisplatin chemotherapy was effective in suppressing chemotherapy-induced emesis for 12 to 24 hours.... Although no placebo control was incorporated into the design of this study, there appeared to be a step up in efficacy from the combined 0.3–1 µg/kg dose group to doses of 3 µg/kg and more. The four highest doses were approximately equally effective when compared with the results from the combined 0.3–1 µg/kg cohort, suggesting a plateau in the dose response for RS-25259 when administered at a dose greater than 3 µg/kg. RS-25259

> was well tolerated in this study. No safety issues related to RS-25259 were apparent.

(Id. at -0055.)

When Helsinn later approached the FDA for permission to commence Phase III clinical trials, these facts and the underlying data reflected in the 2330 study led the FDA to conclude that the 2330 study itself did not provide any reliable dose response data, except possibly at the much higher 30 microgram per kilogram level. See Section I.C.5.

The dosages measured in the Phase II 2330 study were expressed in micrograms of palonosetron per kilogram of patient body weight, i.e., "weight-based" measurements, as stated in the above-quoted passage. At trial there was no dispute that the "3 microgram per kilogram" figure, expressed in that Report, is approximately the numerical equivalent of the 0.25 milligram dose actually claimed in the '219 patent for treatment of CINV. (See, e.g., dkt. 322 at 121.) In the Phase III trials for CINV treatment, described below, Helsinn chose to study "fixed-dose" amounts of 0.25 mg dose and 0.75 mg dose. (See id. at 132.) The 0.75 milligram dose likewise corresponds to the "10 microgram per kilogram" figure in the 2330 study. (See PTX-182.0009 to .0010.)[11]

[11] The following table of conversion equivalents from weight-based dose units to fixed-dose units is contained in the Helsinn Phase III data, and was not disputed at trial:

Weight-based dose groups	Fixed dose groups
0.3 µg/kg – 1 µg/kg	< 0.1 mg
3 µg/kg	0.25 mg
10 µg/kg	0.75 mg
30 µg/kg	2 mg
90 µg/kg	6 mg

(PTX-182.0010.)

The 2330 study was a well-designed study in that it was randomized, double-blind, and multi-center. (See DTX-0227-0014.) On the other hand, as was appropriate for such a Phase II study, it involved only a small number of patients (161 patients, of which 18 were excluded from the efficacy results for valid reasons), and the total number of patients receiving each dose level ranged between only 24 and 46. (Id.)

There was also no formulation data at all in the 2330 study, on stability or any other properties, because the palonosetron was simply diluted in saline solution and buffered for injection. (Id. at -0015; dkt. 324 at 86–89.) In that form, it was not stable at room temperature and required refrigeration and resupply in the course of the study. (Dkt. 322 at 102.) In fact, although the Roche Syntex formulation books contained some research on possible formulations, that work had not progressed to the actual making of any formulations, complete with excipients, that could have been used for Phase III clinical studies. (Id. at 103–04.)

By 1997, as described below, Roche had discontinued work on the Roche Syntex palonosetron project, deciding not to proceed with it after completion of the Phase II studies. (Id.)[12] At that time, Roche made Helsinn aware that Roche was interested in selling a license on the rights to palonosetron and the existing development research. (Id.

[12] The Syntex scientists who had developed the palonosetron hydrochloride compound and taken it through the Phase II stage of development did publish a few materials in the 1995–1998 time period. Those publications were later listed as prior art references in the patents-in-suit. (See, e.g., '724 patent, page 1, listing references by R.M. Eglen, J. Chelly, and J. Tang.) Those references, and a 2001 set of abstracts by Helsinn researcher G. Piraccini (also identified as prior art in those patents), are particularly relevant to the obviousness issues in this case, as discussed in the testimony of the parties' expert witnesses on those issues.

at 80.) After a due diligence period under confidentiality restrictions, Helsinn did enter into that license agreement with Roche in early 1998, and began its work on further development of palonosetron into a pharmaceutical product. (Id. at 31, 49.)

3. Helsinn license from Roche

Plaintiff Helsinn Healthcare S.A. ("Helsinn" or "HHC") is a family-owned and family-run Swiss company with headquarters in Lugano, Switzerland. (Dkt. 320 at 108; dkt. 322 at 76–77.) The Roche pharmaceutical organization is a large corporate entity that also has a headquarters in Switzerland. (Dkt. 322 at 86.) In the 1997–1998 time frame, Roche and Helsinn would periodically communicate about potential licensing arrangements. (Id.) That is how Helsinn was informed that Roche had decided to terminate its palonosetron development project at the conclusion of the Phase II studies and was interested in licensing out the rights to the project. (Id. at 86–87.).

The Helsinn organization at that time had been managed by the founder, Gabriele Braglia, who was transitioning the leadership of the company to his sons, Enrico and Riccardo Braglia. (Id. at 86.) Dr. Giorgio Calderari is a Ph.D. chemist and current group general manager and chief operating officer at Helsinn in Lugano. (Dkt. 320 at 106.) He is a named inventor in the four patents-in-suit. (Id.) He testified at length at trial, called as a witness by both sides. (Dkt. 320 at 105–225; dkt. 322 at 9–175.)

Dr. Calderari recalled that when he joined the organization in 1985, it was a small company with a staff of about 20 employees at Lugano and another 15 employees at its chemical plant in Biasca, Switzerland. (Dkt. 322 at 77–78.) In the 1997–1998 time

period, before Helsinn began its development of palonosetron, its organization had grown to approximately 200–250 employees. (Id. at 78.) Its operations were located as before in Lugano and Biasca, as well as in a finished drug product plant in Ireland at a subsidiary, Helsinn Birex Pharmaceuticals Ltd. ("Helsinn Birex"). (Id. at 77; dkt. 320 at 202.) At that time, its major product was an anti-inflammatory drug that was sold in Europe and South America, but sales were declining because it was going off patent, and Helsinn had no products in the United States pharmaceutical market. (Dkt. 322 at 77, 87.)

The business plan of Helsinn, at the time it licensed palonosetron from Roche in 1998, was described by Dr. Calderari as a "business-to-business" model. (Dkt. 320 at 110–11.) Helsinn would take licenses from others who had developed new chemical entities and continue that development process, while simultaneously seeking partners for eventual worldwide distribution. (Id.) In other words, it was looking to in-license drug development projects and try to take them through to the marketing and distribution stage with others. (Id.) Helsinn was not a drug discovery company at that time, and it did not have its own sales force. (Id. at 111.) Nor did it have its own formulation research and development laboratories. (Dkt. 330 at 7–8.) It would obtain those services from contract research organizations ("CROs") and contract manufacturing organizations ("CMOs"). (Id. at 7.)

When Helsinn was considering the prospect of acquiring the palonosetron development rights from Roche, it had full access to Roche Syntex's laboratory and Phase

II documentation, and it was able to speak with the scientists there. (Dkt. 320 at 114–15; dkt. 322 at 81.) Dr. Calderari was part of the team at Helsinn that was responsible for evaluating that opportunity. (Dkt. 320 at 114.) He testified that the Helsinn team's view of the project, after making its due diligence review, was that from a scientific standpoint it could enable Helsinn to enter a new field of research, and it could be an opportunity for Helsinn to enter the U.S. market, "but we were also aware that there was some risk that we would have to overcome in order to arrive at a successful product." (Dkt. 322 at 87.)

The class of molecules known as 5-HT3 receptor antagonists, commonly called setrons, had already been developed into pharmaceutical products, although none of the setron molecules covered by Roche Syntex's '333 patent had yet been developed to that point. (Id. at 80.) At that time in early 1998, there were already three setron products on the market in the U.S., namely ondansetron, dolasetron, and granisetron. (See id. at 89.) They were sold by major companies including GlaxoSmithKline and Sanofi-Aventis.[13] (Id. at 92.) Those products contained different setron compounds, but Helsinn understood that they were considered interchangeable. (Id. at 91.)

The palonosetron project documents reviewed by Helsinn showed that Roche itself, in view of Syntex's Phase II testing, did not see any particular efficacy advantages of palonosetron compared to the existing setron products, nor did it see market potential. (Id. at 81–82.) So even if Helsinn were to succeed in developing a commercial

[13] Zofran®, or ondansetron, was approved by the FDA for the treatment of CINV in January 1991. (Dkt. 330 at 155.) Kytril®, or granisetron, was approved by the FDA for treatment of CINV in December 1993. (Id. at 156.) Anzemet®, or dolasetron, was approved by the FDA for the treatment of CINV in September 1997. (Id.)

formulation and obtaining FDA approval after Phase III clinical trials, the palonosetron product would be a fourth setron in the same class, a so-called "me too" compound. (Id. at 82.) It would likely earn only modest sales, according to Roche's projections. (Id. at 83.) Furthermore, the earliest of those setrons, ondansetron, was losing its patent protection in 2005. (Id. at 144.) Roche charged Helsinn a relatively modest sum, $10 million, for the license rights to palonosetron, with further royalties due only if and when a product was approved and launched. (Id. at 84.)

Helsinn was also aware, from scientific publications, that at that time many companies including Roche were developing or were looking to another class of antiemetic products called NK-1, referring to neurokinin receptor antagonists. (See id. at 85.) In fact, at a later time, in or about 2005, Roche licensed to Helsinn an NK-1 compound named netupitant, and Helsinn took it from the end of Phase I trials through FDA approval and its launch in the U.S. in 2014. (Id. at 86). Also Roche, even while discontinuing its palonosetron project and licensing it to Helsinn, and while pursuing development of new NK-1 compounds, actually purchased the rights to the patented 5-HT3 product granisetron some years after 1998, paying over $1 billion for that deal as reported in the press. (Id. at 84.)

Aside from predicted poor marketing prospects for the palonosetron project, there were also technical problems confronting Helsinn as it considered whether to in-license the project. (Dkt. 320 at 124–25.) Helsinn studied Roche Syntex's efficacy records at the end of Phase II, including the results of the Phase II study 2330, which was for treatment

of CINV. (Dkt. 320 at 31–32.) In their internal records at the end of Phase II, the Syntex scientists themselves had recommended that for a CINV indication (as contrasted with a PONV indication, which would typically be at a lower dosage), the minimum dose to be selected for Phase III trials should be 1.0 milligram, not the equivalent of 0.25 or 0.75 milligram doses suggested in the 2330 study conclusions. (Dkt. 322 at 111–12.)[14]

The Syntex scientists had also recommended (but not prepared or tested) a formula concentration level of 0.4 milligrams of palonosetron per milliliter of solution for the CINV Phase III trials. (Dkt. 322 at 111.) However, the Syntex formulation studies indicated that "[t]he higher the drug concentration in the solution, the less stable it becomes." (Id. at 113.) So stability itself was an issue, but so were dosage and concentration. (Id.) As Dr. Calderari summarized the situation:

> The problem is that from a chemical point of view, you wish to have the lowest possible concentration ... because this increased the probability of having a stable solution. On the other hand, for showing efficacy, you have to have a dose or a concentration which is enough high [sic] so that the product will be at the end efficacious in the patient.

(Id. at 114–15.)

Keeping in mind all of those considerations, Helsinn did make the decision to proceed with the palonosetron project, entering into the license with Roche in early 1998. (See id. at 49.) As part of that deal, ownership of all the remaining developmental batches of the palonosetron API was transferred to Helsinn. (Id. at 104.) Roche specified

[14] Helsinn's PONV clinical expert, Dr. Keith Candiotti, testified that CINV dosage of setrons was generally higher than PONV dosage. (Dkt. 331 at 85.) Teva's clinical expert, Dr. David Frame, testified to the same effect. (Dkt. 328 at 121–22.)

that those supplies of API could be used only for developmental purposes, including Phase III clinical trials; that API could not be used for a commercial product. Helsinn complied with that restriction. (Id. at 104–05.)

Helsinn began its work under the license agreement with Roche by building a "project team." (Dkt. 320 at 109.) Dr. Calderari was in charge of the "chemistry manufacturing and control" ("CMC") part. (Id. at 109–10.) He explained that involved "developing the API ... drug processes [and] quality control, up to having everything ready for the release and collecting all the necessary chemical stability data for filing a New Drug Application." (Id. at 110.) Dr. Calderari was assisted in those functions by Dr. Daniele Bonadeo, whose degree was in chemistry and pharmacy and who also became a named inventor on the patents-in-suit. (Dkt. 330 at 5–6.)[15]

The dose selection and clinical studies for Helsinn's project were supervised by Dr. Alberto Macciocchi, a medical doctor who was also a Helsinn employee, in consultation with Dr. Calderari and his CMC group. (Dkt. 322 at 48, 119.)[16] There were also chemical people at Helsinn's own API manufacturing plant, and regulatory staff, as part of the Helsinn project team. (Dkt. 330 at 9.) In addition, Helsinn engaged a former Syntex scientist, Thomas Malefyt (another named inventor on the four patents-in-suit),

[15] Dr. Bonadeo was deposed in this action, and portions of his testimony were placed in evidence at trial. (Dkt. 330 at 5–37.)

[16] Dr. Macciocchi passed away in approximately the mid-2000's. (Dkt. 322 at 48.) However, he was still functioning as project supervisor in the clinical area when Helsinn received the first of the Phase III preliminary results and forwarded them to the FDA in early 2002. (Id. at 59–65.) He continued in that same position to the end of Phase III and beyond, and he signed all of the Phase III final Clinical Study Reports. (DTX-0288-0004; DTX-0289-0003; DTX-0290-0003.)

who had been the CMC leader of the Roche Syntex palonosetron project team. (Dkt. 322 at 99–100.) He rendered a consulting report addressing the related issues of stability, dose selection, and concentration in designing the Phase III trials. (Id. at 115–16.) As Dr. Bonadeo testified, "the aim ... was to have an NDA for CINV use of palonosetron." (Dkt. 330 at 9.)

There were substantial communications between the Helsinn project team and the former Syntex researchers, as well as other specialist consultants engaged by Helsinn, during the period starting in 1998 when Helsinn licensed the palonosetron project from Roche Syntex. Much of that work involved studying the Syntex Phase II clinical data and considering what doses and concentrations of palonosetron to recommend to the FDA for Phase III clinical trials.

Helsinn confidential records in that period include minutes of a week-long meeting in Palo Alto, California from July 20 to July 24, 1998 ("1998 Helsinn Clinical Meeting Minutes"). The persons attending that meeting included Dr. Macciocchi and Dr. Calderari from Helsinn; former Syntex researchers including Mr. Malefyt; Dr. David Gandara from University of California Davis, a prominent medical oncologist (see dkt. 324 at 45–46); and other doctors and scientists.

The summary of that meeting, as reported in the Minutes, stated in part:

> **Overview**
>
> .... After much consideration, and pending further statistical analyses of the phase 2 data, the following drug doses and concentrations are proposed for the CINV ... trials.

Dose (5 ml)	mg/ml
0.25 mg	0.05
0.75 mg	0.15
2.0 mg	0.4

....

Planned data analyses

1. A further analysis of the phase 2 data is important, including
   - by sex,
   - µg/kg converted to per mg dosing,
   - splitting the 0.3 and 1 µg/kg doses, and
   - conducting a pk/pd analysis.
2. Safety should be reviewed by mg dosing.
3. Phase 1 volunteer data (pk) should be compared with phase 2 patient pk data.
4. The long half-life should be investigated on a per patient basis.
5. Phase 2 days 2-5 should be analyzed further (and evaluate in comparison with ondansetron days 2-5).

(DTX-0015-0008 to -0009.)[17]

4. The Oread agreements

Helsinn was aware that it would need manufacturing and testing capabilities in order to proceed to Phase III trials. (Dkt. 322 at 123–24.) The immediate need was to be able to create sufficient quantities of an actual formulated composition for use in the Phase III clinical studies. (Id.) That formulation would contain the palonosetron API batch material Helsinn had purchased from Roche, if the FDA agreed. (Id. at 123.) It would also contain the excipients that Helsinn would select for inclusion in the

[17] In the detailed contents of the 1998 Helsinn Clinical Meeting Minutes, it was noted that "Gandara recommended that, despite the unusual result in 2332 [the Phase II study on oral palonosetron for highly emetogenic CINV], 3 µg/kg was most likely the correct dose for CINV." (DTX-0015-0012 (bracketed text added).)

intravenous formulation that would be administered to the Phase III subject patients.[18] That Phase III intravenous formulation would be subject to FDA supervision as to manufacturing quality. (Id. at 135.) It would also have to be tested for properties including quality and stability, with those results reported to the FDA before and during the Phase III process. (Id. at 134–35.)

Looking beyond the Phase III trial period, if Phase III was successful and Helsinn decided to try to market a product based on that IND in the U.S. market, Helsinn would have to file a New Drug Application. One of the many requirements of Helsinn's NDA filing would be to document how and where the applied-for product or products would be manufactured and packaged for commercial distribution. (Id. at 135–36.) In connection with any such NDA, sample batches of commercial product would have to be submitted to the FDA, with full manufacturing documentation. Helsinn would need to arrange for the manufacture of new palonosetron API supplies for commercialization because as noted above, Helsinn's license from Roche did not permit the Syntex-made API supplies to be used in any commercial products.

Even before the license between Roche and Helsinn was finalized in early 1998, Helsinn had entered into a Confidential Disclosure Agreement, dated November 25, 1997, with a company named Oread, Inc. ("Oread") for the purpose of exploring a development and manufacturing relationship ("Oread Confidentiality Agreement"). (See DTX-0391-

[18] According to Dr. Calderari, before Helsinn licensed the palonosetron development project from Roche, Syntex had made the determination to pursue an intravenous formulation for purposes of the Phase III trials. (Dkt. 322 at 23–24.)

0002.) Oread was a company located in California, on the same campus as Syntex. (Dkt. 320 at 159.) It was an entirely separate company, not related to Helsinn. (See id.) Some of the personnel at Oread had come from Syntex, including Kathleen M. Lee, who later was named as one of the inventors on the patents-in-suit. (See DTX-1023-0001; dkt. 322 at 170–71.)

On July 13, 1998, Helsinn and Oread signed a contract entitled "Development and Manufacturing Agreement" ("Oread Development Agreement"). (DTX-0391-0001, et seq.) That Development Agreement expressly incorporated the confidentiality restrictions contained the Oread Confidentiality Agreement. (Id. at -0002.)

There were a number of functions that Oread contracted to perform under that Development Agreement, as generally described in its Exhibit A, Part I, Statement of Work, and as explained in the testimony of Dr. Calderari. (Id. at -0009; dkt. 320 at 172–176; dkt. 322 at 122–30.) Those functions included analytical and formulation development work, as well as taking the Syntex-manufactured palonosetron API owned by Helsinn (located in Boulder, Colorado, see dkt. 320 at 195), and manufacturing "developmental batches" of product formulation. (Dkt. 320 at 176.) That formulation would be used both for Phase III stability and quality testing, and for administration to patients in the Phase III clinical trials. (Dkt. 322 at 134–35.) The Oread Development Agreement also specified that Oread would perform the stability testing on the developmental formulation batches. (DTX-0391-0009.)

The Oread Development Agreement stated that Helsinn would provide sufficient palonosetron API to Oread for the Phase III clinical formulation manufacturing; and the Oread scope of work expressly did not include any API development and manufacture. (Id.) In other words, as Dr. Calderari explained, "we would give our API to them, and they would use them to prepare the ... formulation batches, for then giving us back to prepare to investigate in the Phase III clinical trials." (Dkt. 322 at 123–24.) He also testified that although Helsinn and Oread had discussions about Oread's potential capacity "in helping us in the future manufacturing commercial batches," no such agreement was ever reached. (Id. at 125; see also dkt. 320 at 160–61.)

Helsinn and Oread commenced working together under the Oread Development Agreement dated July 13, 1998, and continued those activities until Oread suddenly went out of business in mid-2000, during the Phase III trials, leaving Helsinn to find a substitute contractor. (Dkt. 320 at 169–70.) The functions that Oread did perform under contract during that period, for which it was paid by Helsinn, are summarized below.

5. FDA meeting March 10, 1999

Armed with all the existing Roche Syntex project information and its evaluations of that information, Helsinn notified the FDA that the Roche Syntex IND 39,797 had been transferred to Helsinn. In a December 23, 1998 submission to the FDA, Helsinn "described plans to develop palonosetron hydrochloride injection for the prophylaxis of ... (CINV), ... summarized palonosetron's clinical development to date and requested an End of Phase II meeting." (PTX-261.0002.) The stated purpose of the meeting was "to get

the Division's input on (1) the planned phase III development program, (2) ... the adequacy of the technology transfer program of drug substance from the Syntex Boulder facility to the Helsinn Switzerland facility, and (3) ... the sufficiency of the preclinical data to support a future NDA." (Id.)

The "End of Phase II" meeting was conducted at the FDA on March 10, 1999, and official minutes of the meeting were prepared by the FDA and distributed to the participants. (Id. at .0001) The meeting was attended by numerous listed FDA representatives, representatives of Helsinn including Dr. Calderari and Dr. Macciocchi, and consultants for Helsinn who were also named in the minutes.[19] In preparation for that meeting, Helsinn had provided the FDA with a "briefing package," and listed questions on which it sought FDA input. (Id. at 261.0002 – .0003.)

Those listed Helsinn questions and the FDA answers, as set forth in the minutes, referred to two proposed Phase III clinical trials named PALO-99-03 and PALO-99-04 that would assess CINV in "moderately emetogenic" chemotherapy. They also referred to the fact that for all Phase III trials, Helsinn's proposed doses were 3 and 10 micrograms per kilogram (i.e., equivalent to 0.25 and 0.75 mg, see n.11 supra). (Id. at 261.0007 –

[19] Two of the consultants listed in the FDA March 10, 1999 meeting minutes were a representative of August Consulting, and a representative of Oread, Inc. (PTX-261.0001.) As Dr. Calderari testified, Helsinn as a foreign corporation was required to communicate and file documents with FDA through an FDA-recognized U.S. representative, and that was the function of August Consulting. (See dkt. 320 at 139.) The Oread representative was present pursuant to the July 1998 Development and Manufacturing Agreement between Helsinn and Oread that Dr. Calderari described in his testimony. See Section I.C.4.

.0008.) There were also proposed trials named PALO-99-05 and PALO-99-06 discussed in the minutes, as more particularly explained below.

The FDA in that meeting, as reflected in the minutes, was adamant that the Phase II study 2330, although named a "dose-ranging, efficacy ... study," had not produced sufficient data to establish what the minimum effective dose of palonosetron in an intravenous pharmaceutical formulation for CINV would be. In the Background section of the minutes, discussing the 2330 study, the FDA stated:

> **Study 2330** was a single-dose, double-blind, parallel, multi-center dose-ranging study in which 161 patients (129 males, 32 females) were randomized to 0.3, 1, 3, 10, 30 or 90 mcg/kg of palonosetron. According to the firm, the objective was to determine dose-response over a wide range of palonosetron doses, using the low-dose levels of palonosetron for control. The primary efficacy measure was the proportion of patients with no emetic episodes and no rescue medication. When compared to the lowest doses (0.3 and 1 mcg/kg) only the 30 mcg/kg dose was statistically significant; a significant dose response trend was not evident.

(PTX-261.0002.)

This FDA minutes statement was referring to the fact that as reported in the 2330 study, at the 3 and 10 mcg/kg levels (equivalent to the 0.25 mg and 0.75 mg dosages that Helsinn ultimately proposed and selected for its Phase III trials), there was no statistical significance to any of the efficacy data in that study. Indeed, according to the FDA at that meeting, the only statistically significant dose level indicating efficacy in the 2330 study for CINV (using a highly emetogenic chemotherapy agent) was 30 mcg/kg, or ten times higher than the 3 mcg/kg dose.

Additional statements in the FDA minutes of the March 10, 1999 meeting emphasized that determining the dose-related efficacy of the proposed palonosetron pharmaceutical formulations would have to abide the results of the Phase III trials. Here are some of those question and answer exchanges:

> Clinical -- Question 5
>
> Are the two trials presented in moderate dose CINV [referring to PALO-99-03 and PALO-99-04], with repeat cycle and pediatric data, considered sufficient to support the label claim, "Prevention of nausea and vomiting associated with initial and repeat courses of emetic cancer chemotherapy"?
>
> - **This question is premature. The program appears adequate, however, all regulatory decisions, including any labeling claims, will be data driven. (Division representatives also noted that a dose response was not shown in Phase II Study 2330, and therefore it is questionable whether the appropriate palonosetron dose has been identified.)**
>
> Clinical -- Question 6
>
> Is [Phase II study] 2330 sufficient to support the label claim "Including high dose cisplatin"? Should a historical control analysis be conducted?
>
> **Note: In the question above, the firm appears to have written "high dose cisplatin" when "highly emetogenic chemotherapy" is what was intended....**
>
> - **Due to the lack of a dose response in this study, these data are inadequate to serve as pivotal efficacy support (although they may be useful as supportive data).**
>
> **(After discussion with the firm, it was agreed that the results of Study 2330 versus a historical control, along with another study in which two doses of palonosetron are compared to ondansetron, then validated by comparison to a historical control could be used to support a claim for palonosetron in the prevention of nausea and vomiting due to highly**

> **emetogenic chemotherapy. Note: Any regulatory decisions will be data driven.)**

(PTX-261.0005 –.0006 (emphasis in original; bracketed text added).)[20]

Similarly, in commenting on the "protocol summaries" Helsinn had submitted before the meeting, with respect to proposed PALO-99-03 and PALO-99-04 trials involving moderately emetogenic chemotherapy, the FDA advised Helsinn:

> **Efficacy data for Study 2330 show that results for the 0.3-1 mcg/kg doses did not differ significantly from the proposed Phase III doses (3 and 10 mcg/kg). Consider including the lower dose as an arm in the Phase III study.**

(Id. at .0008.)

The minutes of the March 10, 1999 FDA meeting also addressed, among other topics, the manufacturing of future commercial batches. The FDA had been made aware that Helsinn proposed to use the Syntex-manufactured palonosetron API in making the pharmaceutical formulations to be used in the Phase III trials, and the FDA expressed concern that for commercialization, the age of that API substance would be problematical. Helsinn replied that they did not plan to use any of that Syntex-made API in manufacturing the commercial batches. The FDA accepted that representation, but made it clear that it would require full disclosure of the planned commercial manufacturing arrangements, as well as commercial product stability data, before it would

[20] As referred to in this quoted text, and as seen in the later-submitted FDA filings, Helsinn was permitted to proceed with just one full-scale Phase III study for the highly emetogenic CINV ("HEC") efficacy, which was PALO-99-05. Helsinn was permitted to submit the re-analyzed results of study 2330, designated PALO-00-01, as the "supportive data" accompanying the PALO-99-05 HEC clinical trial. (See dkt. 322 at 108–26, 134.) Therefore, Helsinn was not required to conduct what would have been PALO-99-06, a second full-scale Phase III clinical trial for HEC efficacy. See n.22 infra.

consider approving a New Drug Application for commercialization of any such product. (See id.) That portion of the minutes stated:

> • **We note your plan to use drug substance manufactured by Syntex (date of manufacture: 1995) for your Phase III drug product. The age of that drug substance is a potential problem.**
>
> **(Note: In response to this comment, the sponsor's representatives indicated that they plan to change the drug substance manufacturer prior to submission of an NDA; Helsinn-manufactured drug substance will be incorporated into the drug product planned for commercial use. The Division's chemistry representative indicated that the information to support this change should be presented clearly and completely in the NDA. He said the Helsinn drug substance manufacturing facility(ies) should be prepared to host an inspection at the time of NDA submission. He also said that three batches of drug product manufactured with Helsinn drug substance should be put on stability; at least one of those batches should be commercial scale.)**

(Id. at .0003.)

Dr. Calderari testified that the Helsinn development team continued to debate internally the questions of what dosage and concentration level or levels to select for the Phase III protocols during this time period. The Helsinn group at that time recognized the fact that the Syntex scientists, at the end of their Phase II work, had recommended a single 1.0 milligram dose for Phase III CINV testing. They were also acutely aware that the FDA said the Phase II 2330 study did not contain reliable dose-related efficacy data. On the dosage issue, when asked how Helsinn ultimately decided to take the two doses that it did select into the Phase III trials, he stated:

> It was ... a big debate. I mean, generally speaking, you tend to run Phase III only with one dose, but as we have seen ..., the FDA was concerned about not having shown this dose efficacy relationship, so our scientists suggested that we should run the Phase III with multiple doses, and I recall that we had a long discussion because Dr. Macciocchi wanted even to have a third

> dose, much higher. Then at the end, we came to a compromise to use these two doses, and this what then was proposed to the FDA in the end of Phase II [March 10, 1999] meeting.

(Dkt. 322 at 119 (bracketed text added).)[21]

Dr. Calderari also explained that the stability issue was also in the forefront of Helsinn's considerations at that time. Although Syntex had recommended a formulation containing 0.4 milligrams of palonosetron per milliliter of solution for a CINV product, there was a concern about stability of the product at that concentration. The Syntex internal documents had identified that "the higher the drug concentration in the solution, the less stable it becomes." (Dkt. 322 at 113, referring to DTX-0254 at 27.) The Syntex inventor Dr. Malefyt, in his September 14, 1998 consulting report to Helsinn, had similarly advised:

> The [P]hase [I and II] IV product required refrigeration. Stability is inversely related to [palonosetron] concentration apparently in both solid and liquid forms. If doses around 10 mcg/kg are required to obtain efficacy for CINV and PONV (both IV or oral liquid capsules), it will be challenging to formulate an IV and oral dosage form that provides sufficient mcg dosage to provide efficacy and also be sufficiently stable.

(PTX-245.0005 (bracketed text added).)

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[21] The March 10, 1999 FDA meeting minutes indicate that at that time, Helsinn had submitted only "protocol summaries" rather than completed proposed testing protocols, and that the doses being proposed at that meeting were expressed in micrograms per kilogram of patient body weight, specifically 3 and 10 mcg/kg. (See PTX-261.0007, .0008.) As discussed below in this Section, when Helsinn submitted its formal proposed Phase III protocols in April 2000, it had decided to simplify the protocols by specifying dosage in fixed-dose milligrams, rather than in relative micrograms per kilograms of patient weight, thus proposing 0.25 and 0.75 mg doses for Phase III. Throughout the trial evidence, including testimony by the parties' experts, those two different measurement forms were discussed in their equivalent values. Thus the parties recognized, for example, that 3 mcg/kg is equivalent to 0.25 mg. (See, e.g., dkt. 322 at 121.)

Dr. Calderari summed up the problem facing Helsinn in trying to achieve a balance between efficacy and stability in creating a Phase III formulation as follows:

> So at the end, this is the dilemma we lived from the -- .... So the dilemma was, me, as a chemist, I wanted -- or my team wanted -- a diluted as much solution, so less concentration (to make sure that at the end we would have had a product that would have been shelf stable), but of course the clinician wanted to use a dosage that was sufficient[ly] high to meet the requirement to treat emesis.

(Dkt. 322 at 117–18 (bracketed text added).)

6. Phase III protocol

Ultimately, Helsinn decided that to balance the documented concerns about efficacy and stability, it would take two different dosages and concentration levels into its Phase III trials for CINV. (See id. at 119.) On April 7, 2000, it submitted to the FDA a set of "safety and efficacy protocols" for Phase III clinical testing designated as follows:

- PALO-99-03 entitled, "A Double Blind Clinical Study to Compare Single IV Doses of Palonosetron, 0.25 or 0.75 mg and Ondansetron, 32 mg IV, in the Prevention of Moderately Emetogenic Chemotherapy-Induced Nausea and Vomiting"
- PALO-99-04 entitled, "A Double Blind Clinical Study to Compare Single IV Doses of Palonosetron, 0.25 or 0.75 mg and Dolasetron, 100 mg IV, in the Prevention of Moderately Emetogenic Chemotherapy-Induced Nausea and Vomiting"
- PALO-99-05, entitled "A Double Blind Clinical Study to Compare Single IV doses of Palonosetron, 0.25 or 0.75 mg and Ondansetron, 32 mg IV, in the Prevention of Highly Emetogenic Chemotherapy-Induced Nausea and Vomiting"

(DTX-0293-0001.)[22]

[22] No PALO-99-06 study was needed, based upon the fact that the FDA allowed Helsinn to re-analyze the results of Phase II study 2330, designate that report as PALO-00-01, and submit it as support for the PALO-99-05 Phase III results. (See n.20 supra; PTX-182.)

As shown in these protocol titles, all three protocols specified using both 0.25 and 0.75 mg doses of palonosetron. The 99-03 and 99-04 studies were directed to moderately emetic CINV ("MEC"), and the 99-05 study was directed to highly emetogenic CINV ("HEC"). The protocols specified that the selected concentrations of palonosetron API in the formulations for all three studies would be 0.05 mg/ml for the 0.25 mg dosage and 0.15 mg/ml for the 0.75 mg dosage. (See dkt. 322 at 108.) These concentrations were sharply lower than the 0.4 mg/ml that Syntex had recommended for the CINV formula. (See id.) The low concentrations were reflective of the goal, as described by Dr. Calderari, to promote stability by decreasing the concentration of palonosetron in the pharmaceutical formulation. (See id. at 113.)

Dr. Calderari was asked why Helsinn chose to bring two doses into each of those Phase III CINV trials, both of which were lower than the 1.0 mg dose for CINV that had been recommended by Syntex. (See id. at 120.) He said, "this was this compromise between increasing the chances of having a stable product from one side, and increasing the chances to have an efficacious product on the other side." (Id.) He explained that the risk that Helsinn took in selecting those relatively low doses for CINV was "that at the end, we would end up with a product that was not efficacious enough." (Id.)

Dr. Calderari testified, under questioning by counsel for Helsinn, that Helsinn did not know whether these lower doses would work for CINV efficacy, prior to receiving the results of the Phase III trials. He stated the reason was "[b]ecause it was not tested

before, and during the Phase III trial, you have absolutely no idea how the clinical trial is going in terms of results." (Id. at 120–21.)

Helsinn itself made an apparently contrary statement, however, in its proposed Protocol No. PALO-99-03, dated November 15, 1999. There, referring to the table of data in the Phase II 2330 study summarizing patients' responses for CINV treatment with doses from 0.3/1 mcg/km to 90 mcg/kg, Helsinn stated, "Data from this study clearly demonstrate that the 3 µg/kg dose of palonosetron is the minimal effective dose in preventing CINV." (DTX-0293-0035.)

Chronologically, that statement was dated in late 1999 and submitted to the FDA in April 2000, despite the FDA's statements to Helsinn in the March 10, 1999 meeting minutes, that "a dose response was not shown in the Phase II Study 2330," and that "only the 30 mcg/kg dose was statistically significant; a significant dose response trend was not evident." (PTX-261.0001, .0005). When queried about it by counsel for Teva, Dr. Calderari testified as follows:

> Q. .... The term "minimal effective dose" is particularly important, isn't it?
>
> A. Well, I am not a medical doctor, but this is standard. I mean, if you want to go to a Phase III clinical trials, it's a fact that you have to have shown some efficacy in Phase II. Otherwise, you cannot jump and you will even not get the approval to go to the Phase III. So, yes, the product was showing some efficacy clearly.
>
> Q. Exactly. In real human beings.
>
> A. Yes.
>
> Q. And efficacy meaning it reduced the likelihood of CINV.

> A. Right. It was giving enough signal for us to take the risk to continue to the Phase III and getting approval from the FDA to move to the Phase III and show if we were really able to show a real efficacy to get an approval by the FDA, but this is standard. You finish the Phase II. You see a some signal. You go with the agency. You discuss, and then if everything is fine, you move to the next step.

(Dkt. 320 at 142–43.)

His testimony on this point was consistent, however, with the actual statements made by Syntex in the 2330 study Final Report, quoted in full in Section I.C.2, where Syntex reported, "**A statistically supported dose-response relationship for efficacy ... between the lowest dose level of RS-25259 and each subsequent higher dose level was not observed in this study**.... Although no placebo control was incorporated into the design of this study, there **appeared to be** a step up in efficacy from the combined 0.3–1 µg/kg dose group to doses of 3 µg/kg and more.... **Based on the results of this study, a dose of 3 µg/kg or 10 µg/kg might be appropriate for further development**." (DTX-0227-0015, -0016 (emphasis added).) This testimony was also consistent with what the FDA had informed Helsinn at the March 10, 1999 meeting, "**Efficacy data for Study 2330 show that results for the 0.3–1 mcg/kg doses did not differ significantly from the proposed Phase III doses (3 and 10 mcg/kg)**." (PTX-261.0008.) "[**A**] **dose response was not shown in Phase II Study 2330, and therefore it is questionable whether the appropriate palonosetron dose has been identified.**" (Id. at .0005.)

Following the March 10, 1999 FDA meeting, Helsinn continued its preparations to file proposed Phase III protocols with the FDA. The documentary evidence described below shows that as of March 24, 1999, Helsinn had already completed developing, on

paper and in actual solution, the 0.05 mg/ml palonosetron concentration, with all measured excipients, that had been described in the Syntex formulation books and was later claimed in the '724, '725, and '424 patents. (The same 0.05 mg/ml palonosetron concentration (with excipient content) was also reflected in the later-issued '219 patent, as the result of dose 0.25 mg palonosetron in 5 ml solution.) (See dkt. 320 at 175–76.)

Dr. Calderari testified that Example 4 in the written description of all four patents-in-suit is an intravenous formulation description that appeared in the Syntex formulation book. (Id. at 152.) Example 4 is reproduced in the margin.[23]

That same formulation, described in the Syntex research materials, had actually been made up into a bulk batch by Helsinn's contractor, Oread, before March 24, 1999. (See, e.g., DTX-1125-0001 to -0006.) This fact was reflected in statutory declarations with supporting documentation later filed in the USPTO during the prosecution of the

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[23] Formulation I

The following is a representative pharmaceutical formulation containing palonosetron that is useful for intravenous formulations, or other liquid formulations of the drug.

Ingredient	mg/mL
Palonosetron Hydrochloride	0.05*
Mannitol	41.5
EDTA	0.5
Trisodium citrate	3.7
Citric acid	1.56
WFJ [water for injection]	q.s. to 1 ml
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 ± 0.5

*calculated as a free base

('724 patent, col. 7, lines 47–66 (bracketed text added).)

patents-in-suit and related patent applications. One such example, under the application that led to issuance of the '724 patent, was a declaration of named inventors Calderari, Bonadeo, Cannella, and Enrico and Riccardo Braglia dated November 21, 2007. (DTX-0004-0001 to -0005; see also DTX-1125, a similar Bonadeo declaration dated Feb. 13, 2007, containing the two-page Exhibit A documents referred to in this series of declarations.)[24] That declaration stated, inter alia, as follows:

> 5) This patent application is based on the discovery of liquid formulations of palonosetron with improved stability.
>
> 6) The formulations can be stored for prolonged periods of time in a variety of conditions without significant degradation or loss of potency, and thus are considered pharmaceutically stable.
>
> 7) The formulations were developed by us at Helsinn in the late 1990s, and were completed sometime before March 24, 1999.
>
> ....
>
> 14) The Example 4 formulation was developed by us sometime before March 24, 1999 and transmitted to a contract manufacturer for Helsinn, Oread Laboratories in Palo Alto California ("Oread") for the production of commercial scale batches of palonosetron hydrochloride.
>
> 15) A copy of the master batch record developed by Oread for the formulation is contained in Exhibit A hereto.
>
> 16) The master batch record describes the Example 4 formulation....

[24] During the prosecution of the USPTO applications that led to issuance of the '724, '725, and '424 patents, Helsinn submitted declarations signed by named inventors Dr. Calderari, Daniele Bonadeo, Roberta Cannella, and Enrico and Riccardo Braglia (the names of the latter two Helsinn executives were subsequently deleted as inventors per U.S. inventorship requirements). There were several such applications in the patent family history, and those declarations were similar in content but filed under various patent application numbers. (See generally dkt. 289 (chart: Family Tree of Patents at Issue).) Examples of those declarations are in evidence as DTX-0004, DTX-0287-0413, and DTX-1125.

17) As can be seen, the batch record has an effective date of March 24, 1999, and thus makes clear that we developed the formulation before this date.

18) In fact, we had invented and were in possession of all of the subject matter currently claimed in ... [the applications for the '724, 725, and '424 patents] as of March 24, 1999, because we had completed stability studies for the Example 4 formulation, and understood the effect that variations in palonosetron concentration, pH, and excipient concentrations would have on the stability of the formulation.

(DTX-0004-0001 to -0003 (bracketed text added).)

Dr. Calderari described that when he took over the role for the development of palonosetron at Helsinn, he had to read a variety of results from Syntex. He said that Syntex's formulation book, describing various formulations including Formulation 4, was "where they describe their attempt, their experiment to arrive to a formulation that might be suitable for clinical trial and then after for commercialization. But to my surprise, when I made the first due diligence, they had never manufactured that formulation, that they had absolutely no ... data about the stability of potential formulation to be used in a clinical trial." (Dkt. 320 at 116.) Furthermore, he stated that the Example 4 concentration formulation of 0.05 mg/ml was recommended by Syntex to be used in Phase III clinical trials for PONV efficacy (then called "Formulation 90"). (Id. at 116–17.) On the other hand, Syntex had recommended a Phase III palonosetron concentration formulation of 0.4 mg/ml for CINV efficacy (then called "Formulation 89"). (Dkt. 322 at 111–12.)

Dr. Calderari also testified that as to the written description of the Example 4 formulation, as embodied in the actual developmental formulation batches prepared by

Oread, the inventor statement that he and the other inventor declarants signed, that "the formulations ... were completed sometime before March 24, 1999," was a true statement. (Dkt. 320 at 149.)[25] He stated, "[e]xactly, and this is exactly what we have completed at that time. We have completed the selection of the formulation that we will then go and test for stability and for the clinical trial. This is what we had completed at that time." (Id. at 150–51.) He had the same answer regarding the statement at the end of the inventor declaration, "we had invented and were in possession of all of the subject matter currently claimed." (DTX-0004-0003.) In his words, "we [had] completed the specification, the selection of this formulation to then be tested in stability studies and in human beings." (Dkt. 320 at 155.)

Helsinn's decision to proceed to CINV Phase III clinical trials with fixed doses of 0.25 mg and 0.75 mg in 5 ml vials was made following the March 10, 1999 FDA meeting (in which a range of doses was discussed, in the weight-based measurements (mcg/kg) used in the Phase II studies), as reflected in the Phase III protocols subsequently submitted to the FDA. (See, e.g., DTX-0293-0001; dkt. 322 at 132.) Dr. Calderari testified that as part of those dosage selections for Phase III, Helsinn decided on corresponding palonosetron concentrations of 0.05 mg/ml and 0.15 mg/ml, which were both lower than the 0.4 mg/ml concentration that Syntex had recommended for CINV Phase III trials. (Dkt. 322 at 108.)

[25] The other inventor declarants, Dr. Bonadeo, Dr. Cannella, and Dr. Braglia, all testified consistently that the statement made regarding the Example 4 formulation was true at the time that they signed the declaration. (See dkt. 330 at 22–23, 41–42, 66.) None of the inventor declarants sought to add any testimony beyond their prior recollection. (See id.)

While Helsinn was preparing to submit its completed Phase III safety and efficacy protocols to the FDA, which occurred on April 7, 2000 as described below, Helsinn was communicating with the FDA regarding stability testing of the development formulation lots that Oread had prepared (in the selected palonosetron doses of 0.25 mg and 0.75 mg and concentrations of 0.05 mg/ml and 0.15 mg/ml). A letter from Helsinn to the FDA dated August 19, 1999 stated: "Six month stability data for development lots indicate that the Phase 3 formulation is expected to remain stable for a minimum of 18 months, when stored at 25°C and protected from light. We commit to monitor stability of the clinical material and to resupply the drug product as appropriate, to ensure that the clinical material has the identity, quality and purity it purports to have." (DTX-0999-0002.) Dr. Calderari said this was "the formulation we pick[ed] up and we improved, we optimized, and we ran at Oread, and by the time we made the submission, we have six months' stability data." (Dkt. 322 at 163.)

The formal Phase III safety and efficacy protocols for PALO-99-03 and PALO-99-04 (two MEC studies) and PALO-99-05 (one HEC study) were submitted to the FDA by letter dated April 7, 2000, under the existing IND number 39,797. (DTX-0293.) At that time, Oread was still performing its contractual functions in support of the trials. For example, a memo from Oread to Helsinn dated April 10, 2000 described "two phase 3 clinical lots" manufactured by Oread in March and April 1999, containing either 0.05 mg/ml or 0.15 mg/ml palonosetron, in 5 ml glass vials according to the Phase III specifications. It reported chemical and physical stability based on up to 6 months of

available data, and "[t]he stability monitoring of these two clinical lots is continuing according to the protocol." (DTX-1027-0038.) Dr. Calderari confirmed that Oread did provide clinical supplies of the formulation that is covered by the patents-in-suit for Helsinn, in preparation for conducting the Phase III trials, and Helsinn paid Oread for those batches. (Dkt. 320 at 179–82.)

The INTRODUCTION section of the formal Protocols for all three Phase III clinical studies, PALO-99-03, PALO-99-04, and PALO-99-05, contained the following types of statements:

> Results achieved in Phase II CINV studies suggest that palonosetron is safe and effective in preventing nausea and vomiting following emetogenic chemotherapy, especially during the first 24 hours after administration.
>
> Given the high affinity of palonosetron for the 5-HT3 receptor and efficacy results in both animal models and in Phase II studies, a single dose of palonosetron is expected to control acute CINV following moderately and highly emetogenic chemotherapy. Furthermore, due to the long half-life of palonosetron in humans, a single dose of palonosetron may also be beneficial in controlling the delayed phase (24-120 hours) of nausea and vomiting induced by a chemotherapeutic regimen. This study is designed to support the hypotheses that palonosetron is not inferior to currently available 5-HT3 receptor antagonists and is effective in preventing nausea and vomiting following moderately emetogenic chemotherapy....

(See DTX-0293-0030 (PALO-99-03); see also id. at -0149 (PALO-99-04); id. at -0257 (PALO-99-05, replacing "moderately emetogenic" with "highly emetogenic").)

7. Commencement of Phase III trials

All three Phase III clinical trials were performed by a German contract research organization named Kendle GmbH & Co. ("Kendle"). (See DTX-0293-0001 to -0007; DTX-0288-0003; dkt. 322 at 54.) The April 7, 2000 protocol application specified that

the "name and title of the person responsible for monitoring the conduct and progress of the clinical investigations" was Alberto Macciocchi, MD, Senior Manager, Product Development at Helsinn. (DTX-0293-0004.) Dr. Macciocchi was still in that position as of July 19, 2002, the date of the Clinical Study Report for the earliest-completed trial, PALO-99-03. (DTX-0288-0003 to -0004.) See n.16 supra.

The patient participation in the three Phase III clinical trials began with the earliest of those trials, PALO-99-03. According to the Clinical Study Report at the end of that trial, the Study Initiation Date ("first patient in date") for PALO-99-03 was August 1, 2000. The Study Completion Date ("last patient out date") for that trial was October 2, 2001. (Id. at -0003.) Neither of the other two Phase III trials had a data "locked" date prior to the critical date of January 30, 2002. See Section I.C.11. Therefore, much of the evidence in this chronology focused on the progress of PALO-99-03.

In September 2000, just as the first of the three Phase III clinical trials began, Helsinn issued a press release entitled "Helsinn Announces That Patient Enrollment For Phase III Palonosetron Trials Progresses Both in the USA and Europe." (DTX-1227-0001.) That publication stated, inter alia:

> "The Phase II trials demonstrated the efficacy of Palonosetron in the prevention of emesis with no significant side effects...," said Luigi Baroni M.D., Director of Scientific Affairs. "We are now eager to complete the data necessary for NDA filing scheduled for early 2002."

(Id.)[26]

[26] The September 14, 2000 Helsinn press release also stated: "'Upon market approval, Helsinn will be in a position to supply its marketing partners with a finished product ready for distribution,' said Giorgio Calderari, Director of Technical Affairs. Helsinn is seeking marketing

8. The SP agreements

Returning to the topic of contracting, it will be recalled that Oread had suddenly closed down in or about June 2000, just before the Study Initiation Date for PALO-99-03, and with the other two Phase III clinical trials gearing up as well. As a result, Helsinn needed to find another organization to pick up Oread's functions and move forward with it in the development project. Dr. Calderari testified that Helsinn then hired SP Pharmaceuticals L.L.C. ("SP"), "essentially, ... to finish the work that we started with Oread...." (Dkt. 320 at 196.)

A document later submitted to the FDA as part of Helsinn's NDA filing summarized that portion of the drug product development history as follows:

> Oread ... was selected as the manufacturing site for the formulation of the injectable solution for Phase 3 clinical supplies and for the manufacturing of commercial batches (reference IND amendment serial #064, 19 August 1999). A Commercialization Development Plan was agreed with the Agency during the End of Phase 2 Meeting, 10 March 99, and enacted to complete the transfer of the manufacturing technology for the optimized drug product formulation from Syntex to Oread, Inc.
>
> Due to the subsequent closure of the Oread manufacturing facility in June, 2000, SP Pharmaceuticals, Albuquerque, New Mexico, was selected as the site of manufacture for future NDA commercial drug product, as well as additional Phase 3 clinical batches. No significant changes in the manufacturing process or equipment occurred with the site transfer. Reference is made to IND Amendment Serial #95, 22 Nov. 2000, which

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partners for this patented product in different territories." (DTX-1227-0001.) The reference to "seeking marketing partners" is a topic covered in the trial evidence in some detail, as discussed in Section I.C.9. The words "patented product" appear to relate, at least in the United States, to the original '333 genus patent on the palonosetron molecule, which would not expire until 2015.

> was submitted in support of SP Pharmaceuticals as the site of manufacture for commercial product.

(DTX-0310-0005, -0006 (footnotes omitted).)[27]

Dr. Calderari stated that Helsinn's contractual relationship with Oread never advanced to the point of any serious negotiations or contracting regarding Oread as a manufacturer of any palonosetron commercial product (despite Helsinn's apparent designation of Oread to the FDA in March 1999 as the "selected" site for such manufacturing). (Dkt. 322 at 125–26.) Dr. Calderari characterized the Oread agreement as a "fee for service agreement." (Id. at 122.) Nevertheless, the above-quoted FDA filing statement indicates that during the Phase III process, Oread was at least identified by Helsinn to the FDA as the "selected" site for future commercial manufacturing.

The first agreement that Helsinn entered into with SP, even before Oread totally stopped functioning, was a Secrecy Agreement dated April 10, 2000. (PTX-361.) It was followed by a "Letter of Intent" designated "Confidential" ("SP Letter of Intent"). (DTX-0258-0002.) The SP Letter of Intent was signed by SP on October 19, 2000, and was signed by Dr. Calderari for Helsinn on November 7, 2000. (Id. at -0004.)

The SP Letter of Intent stated that the parties were "in the process of negotiating a Master Services Agreement for development or manufacture of pharmaceutical products," and they agreed that SP would begin such work, subject to the terms of the Letter of Intent and any Scope of Work documents they would mutually agree to in writing. (Id. at

[27] The Helsinn agreements with SP, referred to in this quoted FDA filing, are described below in this Section.

-0002.) Attached to the Letter of Intent, signed by the parties on the same dates as the Letter of Intent itself, was a Scope of Work description (id. at -0006 to -0020), and an Appendix A: Pricing and Technology Transfer. (Id. at -0021 to -0023.)

The Scope of Work stated, among other things, that SP "will manufacture Product meeting the Specifications ... and perform such other responsibilities detailed" therein. (Id. at -0006.) It described that Helsinn would "furnish SP with sufficiently tested and released API to guarantee filling the theoretical batch size...." (Id.) It stated that SP would furnish the vials and the listed incipient raw materials (the EDTA, mannitol, citric acid, etc.), along with related documentation, and would "manufacture the product according to the approved master batch record." (Id. at -0010.) It also provided that SP would do specified quality testing on the finished products, described as 0.05 mg/ml and 0.15 mg/ml (id. at -0012, -0013), and would do stability testing on "Product: Palonosetron-HCl IV injection 0.25 mg/vial & 0.75 mg/vial." (Id. at -0013, -0014.) Among other provisions, it also stated:

> **J. Commercial Product Validation**. SP will perform the following process validation, manufacturing and stability activities to prepare for product commercialization.
>
> 1. Manufacture 3 lots of up to 50,000 vials of Palonosetron-HCl intravenous injection for commercial product validation and sale.
>
> ....
>
> 2. Perform stability studies on the commercial product validation lots.
>
> ....

(Id. at -0015.) There was also an Appendix A: Pricing and Technology Transfer, describing some batches that were going to be manufactured by SP and a price for those

batches, including "[m]anufacture up to 10,000 vials of the ... finished drug product." (Id. at -0021, -0022.)

Dr. Calderari testified that the SP Letter of Intent and attached Scope of Work document did not actually provide for SP to manufacture any commercial product for Helsinn. (Dkt. 322 at 129.) He explained that it provided that Helsinn would pay SP for each activity mentioned in the Scope of Work, including to manufacture the batch size Helsinn was requiring them to manufacture at the time. (Id.) He said that the purpose of the SP Letter of Intent was "a development agreement to make some batches, to test them, to put on stability, and possibly to use in clinical trials." (Dkt. 320 at 196.) He confirmed that SP did actually do the work of creating development batch lots and clinical lots under the SP Letter of Intent. (Id.)

Dr. Calderari said that it was only after the critical date, on June 24, 2002, that Helsinn and SP entered into an agreement for future commercial manufacturing. (Dkt. 322 at 129.) That agreement is identified in the margin.[28] It is undisputed, however, that as part of its eventual NDA filing, Helsinn recounted that as of November 22, 2000, Helsinn had filed an amendment to its Phase III IND application informing the FDA that "SP Pharmaceuticals, Albuquerque, New Mexico, was selected as the site of manufacture

[28] On June 24, 2002, a formal Development and Manufacturing Agreement was entered into between SP and the Helsinn subsidiary in Ireland, Helsinn Birex Pharmaceuticals Ltd. (DTX-0259.) That Agreement also contained confidentiality provisions. (Id. at -0024, -0025). At that time, any FDA approval of a Helsinn palonosetron product was still in the future, but this Agreement set the terms for that eventuality. (See id. at -0003, defining "Commercial Product" as "the Product once it has been approved by a Health Authority for commercial marketing in a Territory.")

for future NDA commercial drug product, as well as additional Phase 3 clinical batches." (DTX-0310-0006.) See n.27 supra and accompanying text. The NDA contained, as required, detailed descriptions of the "Selected Manufacturing Process" that SP would perform to make the proposed commercial product, as well as an explanation of the differences between that commercial process and the manufacturing processes SP would use to make "registration batches," that is, clinical trial formulations. (See DTX-0310-0241 to -0243.)

Dr. Calderari explained that as part of the Phase III clinical trial process, the FDA required Helsinn to show three batches of product formulation manufactured at the intended site of commercialization, tested for at least 12 months of stability. He said the FDA would not consider the Oread stability data for that purpose because Oread was no longer the intended site of commercialization. Therefore, the FDA required three batches made at the SP site to be tested for stability, to demonstrate quality control at the SP plant before Helsinn could submit an NDA application. He recalled that process was accomplished using SP, at its manufacturing site, and Helsinn had that stability data available in approximately the second half of 2002. (Dkt. 322 at 155–56.)

9. The MGI Agreements

The topic of contracting continued to be a feature of Helsinn's drug product development process after the first of the Phase III clinical trials began on August 1, 2000. Having secured, on a confidential basis, the assistance of first Oread and then SP for the functions those companies performed, Helsinn was also simultaneously in search

of "marketing partners," as announced in its September 14, 2000 press release. See n.26 supra.

Riccardo Braglia, who succeeded his father as CEO of the Helsinn companies, testified (in deposition excerpts in evidence) that their business model is "to licensing-in, develop, and licensing-out." (Dkt. 330 at 54.) He said "we are looking to opportunities of product which are in the ... early stage of development or middle stage of development, and also are good opportunities." (Id.)

He mentioned two goals of the licensing-out efforts for the palonosetron project: first, to bring in license fees and thus minimize financial risk of such huge investments for Helsinn, and second, to plan for marketing and distribution of product in the United States after FDA approval. (Id. at 54–64.) He said that the "commercial partner" agreement that Helsinn normally did with its partners around the world would feature an up-front payment to Helsinn when the agreement was signed, as well as "milestone" payments (also to Helsinn) at certain points in the development or filing or approval of certain products. (Id. at 57.) He added that for the palonosetron project, as Helsinn discovered the process was much more costly than anticipated, "the strategy was to find as soon as possible a partner that will give us some milestones [i.e., milestone payments] for the ... licensing rights to the U.S. market." (Id. (bracketed text added).)

Helsinn conducted a lengthy and arduous search for a willing "commercial partner" for the U.S. market, described by Helsinn employee Dr. Rachid Benhamza at trial, which resulted in written agreements with MGI Pharma, Inc. ("MGI"), a Minnesota

company. (Id. at 82–149.) Those agreements, both effective on April 6, 2001, were a License Agreement between MGI and Helsinn (DTX-0115) ("MGI License Agreement"), and a Supply and Purchase Agreement between MGI and Helsinn Birex, the Irish subsidiary. (DTX-0261 and DTX-0311 (same) ("MGI Supply Agreement").)[29]

Dr. Calderari, who participated in negotiating those agreements, described the general nature of the License Agreement as follows:

> [I]t's our standard practice that we grant the rights to a company to explore a patent, and with this, they pay us some licensing fees, and they then will pay us for future royalties on the sales. Concomitant, but subject to this licensing agreement, we also make a supply and purchase agreement that we set the stage for future supplies, once we arrive to get an approval, and also there the price is subject to the price that the company will achieve selling the product on the market. Now, of course, if the license agreement is not there because the product would have been unsuccessful in Phase III, then the supply agreement would not be there.
> ....
> [F]or MGI, it was quite clear that this was a developmental .... product, so they were not buying a product. They were buying the rights to participate in the development effort to potentially have a product in the future.
> ....
> They paid licensing fees for the licensing agreement, for granting the right, for entering in the agreement.... And that helped to continue ... the clinical trials, because we were still doing the clinical trials....

(Dkt. 320 at 212–14.)

His testimony about the nature of the MGI Supply Agreement, under questioning by counsel for Teva, stated in pertinent part:

> Q. Let's go ... to the Supply and Purchase Agreement, DTX-0311.... So here we're talking about purchasing products; is that right?

[29] The MGI License Agreement recited that the parties had entered into a Secrecy Agreement on May 25, 2000, and a Letter of Intent on October 5, 2000, under which they had exchanged confidential information and performed due diligence. (DTX-0115-0004.)

A. Yes. This would set the stage of future purchase of product in the event that we would get to an approval of one or the other, if any, of the formulations that we were studying in the clinical trials.

....

Q. .... It says, in 2.1, "Throughout the term of this agreement, ... MGI undertakes to purchase exclusively from HBP" .... "and HBP undertakes to sell to MGI, MGI's entire requirements of the products to be distributed, promoted, marketed and sold by MGI or MGI's affiliates under the License Agreement." That's what the agreement was?

A. Yes. In case there would have been sales, then they would have to purchase from HBP.

....

Q. [W]e just looked at IND 39,797, Amendment 64 .... And it set forth two ... possibilities for a product, one of which was the formulation that is set forth in the patent in this case, is that right?

....

A. In the IND 39,797, they will describe two products, 0.25 and 0.75 milligrams.

Q. And one of them, the .25, is the formulation that's contained in the patents that are at issue in the lawsuit; is that right?

A. Correct.

Q. ... it says that whatever will be the product that would be approved -- registration ... means market approval -- then we will supply whatever will be the product that will be approved.

Q. Right. And it says what the current products are?

A. Yes. This is a description of the current product that were ... in this Amendment, in the clinical trials.

Q. Which you're seeking approval on at the time you signed this agreement?

A. We were, but we were making the clinical trials, yes.

Q. And which you expected to get approval on?

A. Well, we had the hope. I mean –

Q. Well, you wouldn't have entered this agreement if you didn't expect to get approval, right?

A. No.

Q. And so the products, ... if you look at Article 2.1, that's the definition of products, and then it says, "MGI undertakes to purchase exclusively from HBP," ... and HBP undertakes to sell to MGI, MGI's entire requirements of the products." That's what the agreement is about?

A. Yes. The product that would be approved, yes.

Q. And a price was agreed to, or a pricing scheme was agreed to with respect to these products? Isn't that correct?

A. Yes.... It was setting the stage for the future -- I mean, for regulating the purchase process when the product would have been approved, if approved.

(Dkt. 320 at 210–19.)

The definition of "Products," identical in form in the MGI License Agreement and the MGI Supply Agreement, stated:

> "Products" means the pharmaceutical preparations for human use in I.V. dosage form, containing the Compound as an active ingredient [referring to palonosetron hydrochloride] in the formulation which will be described in the Registration [defined as regulatory approval to market the Products]. The current formulation as submitted to the Food and Drug Administration ... in the IND 39,797 Amendment #64 ... is described in the [First Appendix of MGI Purchase Agreement; Third Appendix of MGI License Agreement] hereto.

(DTX-0115-0007 (License Agreement); DTX-0311-0006 (Supply Agreement) (bracketed text added).)

The Appendix referred to in the above-quoted definition, identical in both Agreements, read as follows:

> **THE PRODUCTS**
>
> Qualitative description of the Products as submitted to the United States Food and Drug Administration under IND 39,797 Amendment #64....
>
> 1. Palonosetron HCl Intravenous injection is supplied as a sterile, isotonic solution in 5 ml Type I clear glass vials each containing 5 ml of product. The product is clear and colorless solution, and contains the equivalent of either 0.05 mg/mL or 0.15 mg/mL of Palonosetron free base. The formulation also contains mannitol as a tonicifying agent, edetate disodium as a chelating agent and citrate buffer to maintain the pH of the solution at the target pH of 5 (±0.5).
>
> 2. The product is terminally sterilized.

(DTX-0115 (License Agreement) at 84; DTX-0311 (Supply Agreement) at 28.)

Both Agreements also contained parallel and mutual confidentiality provisions, of which the following text is representative:

> MGI shall treat as strictly confidential, and shall use solely for the purpose of and in accordance with this Agreement, any and all information, data and/or document received hereunder ... not generally known to the trade (all hereinafter referred to as the "Confidential Information"). MGI shall not make such Confidential Information available to any third Party, including any of its Affiliates, except to competent government agencies to which it will be necessary to disclose such information, and in this case (a) strictly to the extent requested by said agencies and (b) only upon exercise of its best efforts to cause said agencies to maintain confidentiality.

(DTX-0311 (Supply Agreement) at 18.)

MGI Pharma, Inc., is a publicly-traded company required to file SEC disclosures. A published SEC Form 8-K reported:

> On April 6, 2001, MGI PHARMA, INC. ... announced that it had entered into definitive agreements with Helsinn ... pursuant to which Helsinn granted to the Company exclusive license and distribution rights to the product candidate palonosetron in the United States.... Under the terms of the license agreement, the Company will make $11 million in initial payments, ... and will make additional payments to Helsinn based on the achievement of development milestones. The Company will also pay royalties to Helsinn based upon set sales. Under the terms of a related supply agreement, an affiliate of Helsinn will supply the Company's requirements of finished product. The Company will pay the affiliate product supply fees based upon net sales. The term of each of the agreements is ten years from the launch of the commercialized product, unless earlier terminated by the parties.

(DTX-0367-0002.)

Redacted copies of the MGI License Agreement and the MGI Supply Agreement were attached as exhibits to that Form 8-K report. The Appendix to each agreement that identified "**THE PRODUCTS**," quoted above, was not attached to that public filing. (DTX-0367 (passim).) What was attached as an exhibit to the MGI Form 8-K report, and incorporated into that Form 8-K report, was the press release dated April 10, 2001 announcing the execution of those agreements, quoted in the margin. (See DTX-0367-0002.) Neither the publicly disclosed MGI Form 8-K documents nor the Helsinn/MGI April 10, 2001 press release disclosed the formulations being tested in the Phase III trials.[30]

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[30] The April 10, 2001 press release stated, inter alia,

> **Palonosetron is a potent and selective 5-HT3 antagonist with an extended half-life, in Phase 3 development for the prevention of chemotherapy-induced nausea and vomiting** (CINV). Completion of Phase 3 trials could allow for NDA (New Drug Application) submission in the first half of 2002. When launched, palonosetron will compete in the $1 billion North American CINV market.

10. Status of Phase III clinical trials on January 30, 2002

The designs of the three Phase III clinical trials were similar, with differences in the comparator drug (ondansetron in Studies 99-03 and 99-05; dolasetron in Study 99-04) and in the nature of emetogenic chemotherapy agent (moderately emetogenic in Studies 99-03 and 99-04; highly emetogenic in Study 99-05). (See DTX-0293-0001.) Each of those studies was designed with the two selected palonosetron dose levels of 0.25 mg or 0.75 mg. (Id.) The CRO responsible for the trials was identified as Kendle International Inc., with headquarters in Munich, Germany and Cincinnati, Ohio. (See, e.g., DTX-0293-0036.)

The Study Design section of the PALO-99-05 protocol, which was representative of the designs for the other two Phase III trials, summarized the design of that study as follows:

> This is a multicenter, Phase III, randomized, balanced, controlled, double-blind, double-dummy, parallel, stratified, and active comparator study design comparing the efficacy, safety and tolerability of single IV doses of palonosetron, 0.25 mg or 0.75 mg, with a single IV dose of ondansetron 32 mg, in the prevention of highly emetogenic chemotherapy-induced nausea and vomiting. The active comparator, ondansetron 32 mg, is the FDA-approved IV regimen for the prevention of nausea and vomiting following highly emetogenic chemotherapy. This dose is also used in Europe for the prevention of CINV. Implementation of published historical placebo controls will be used to validate the trial, demonstrating its sensitivity. It is

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> ....
> Based on the extended half-life of palonosetron and the results of the Phase 2 trial, its efficacy will be assessed over Day 2 through Day 5 following treatment, in addition to the primary efficacy measure of complete response during the 24-hour period after the start of chemotherapy.

(DTX-1022-0002 (emphasis in original).)

> anticipated that 80 investigative centers will participate in this study; 40 centers in Europe, 35 centers in the United States and 5 centers in Canada. The list of the investigative centers will be distributed to all parties involved in the trial.

(DTX-0293-0263.)

The first-completed Phase III trial was PALO-99-03, as previously stated, with a "last patient out" date of October 2, 2001. (DTX-0288-0003.) The "last patient out" date of PALO-99-04 was December 27, 2001. (DTX-0289-0002.) The "last patient out" date of PALO-99-05 was December 31, 2001. (DTX-0290-0002.)

The final reports of those studies, entitled "Clinical Study Reports," were all dated after January 30, 2002, as described below. See Section I.C.11. Contents of those final reports, however, gave information about the designs and procedures of the studies when the studies were approved by the FDA initially, and later amendments.

The Clinical Study report for PALO-99-03 stated that there were 571 patients enrolled, in 58 active testing centers: 16 centers in Germany, 10 in Italy, 2 in the United Kingdom, 7 in the Netherlands, and 23 centers in Russia, subdivided by region in Arkhangeisk, Moscow and St. Petersburg. (DTX-0288-0006.)[31]

[31] The comparable portion of the PALO-99-04 Clinical Study Report stated there were 592 patients enrolled, and 61 study centers in the United States and Mexico. (DTX-0289-0005.) Likewise, the PALO-99-05 Clinical Study Report said it had 680 patients enrolled, and 76 centers in Europe, Russia, United States/Canada, and Mexico. (DTX-0290-0005.)

The PALO-99-03 Clinical Study Report, in its Synopsis, also gave an overview of the statistical methods chosen to analyze the data generated in the clinical trials, as quoted in the margin.[32]

The evidence presented at trial established that the following sequence of events occurred during the period of time between the PALO-99-03 "last patient out" date, October 2, 2001, and the critical date (for on-sale bar purposes) of January 30, 2002.

An explanation of some of the PALO-99-03 documents was provided at trial by Helsinn expert witness Dr. Carl Peck. He is an M.D. with experience in internal medicine, pharmacokinetics and biostatistics, whose background included a six-year

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[32] The PALO-99-03 Clinical Study Report contained a Synopsis that described the statistical methods used in analyzing the data, stating in part as follows:

> The primary efficacy variable was the proportion of patients considered to have achieved a complete response during the first 24 hours after administration of chemotherapy. The analysis based on the ITT cohort [563 patients] was considered as a primary analysis. To demonstrate the non-inferiority of at least 1 dose of palonosetron to ondansetron, the lower bound of the 97.5% confidence intervals (CI) for the difference (palonosetron minus ondansetron) between the proportion of patients with complete response (CR) during the first 24 hours after administration of chemotherapy was calculated and compared to the pre-set threshold (-15% difference). Moreover, to investigate the equivalence of the 2 palonosetron doses with respect to CR (0 to 24 hours) the bound of the two-sided 95% CI of the difference between the proportions of CR (0 to 24) were compared to the pre-set threshold (±15%). The validation/study sensitivity as assessed by comparing CR (0 to 24 h) of the active control ondansetron with modeled historical placebo results and modeled historical ondansetron results from the literature. Complete response at further time points was analyzed using the same statistical methods as for the primary efficacy parameter. Complete control and the proportion of patients receiving rescue medication were analyzed using the Chi-square test. Furthermore, Poisson regression analysis was performed for the emetic episodes taking into account if rescue medication was administered. Quality of life, number of emetic episodes, severity of nausea and patient global satisfaction were compared between the treatment groups using the Kruskal-Wallis test or the Wilcoxon test.

(DTX-0288-0008 (bracketed text added).)

period as the director of the FDA's Center for Drug Evaluation and Research ("CDER"), the division with responsibility for all drug applications for human administration. He also has a current "special government employee" consulting status with the FDA. (Dkt. 337 at 4–16.)

Reviewing the PALO-99-03 files in evidence and the underlying documentation, Dr. Peck described the work that was done after the clinical study with patients closed on October 2, 2001. Here is his summary of the next few steps in the PALO-99-03 process after that "last patient out" date:

> There is no fully assembled, blinded or unblinded data set at that moment. That's a milestone in the execution of a clinical trial, and if you think about it in a multi-center, multi-national clinical trial, there's a lot to do with respect to gathering the data from each site, making sure that the data has been entered properly. In this case, I have read in the protocol that all the data was collected on handwritten case report forms, so those had to be translated into a computer. They used a double entry system, meaning that two independent persons take the data from the case report form and put it into the computer. Those have to be assembled in each center, then they have to be sent to the CRO, Kendle in this case in Munich, which will assemble them all, and then ... begin to evaluate the quality. This is all well articulated in the protocol, because regulatory agencies and a POSA would require that if you're going to analyze the data for this purpose, it's got to be high quality. It's got to be verified. The company was even doing site visits during that period of time at some of the sites. In fact, one collection of sites was in Russia. One was up near the border of Siberia, and there was a site visit on that very site after the last patient out in order to validate that everything had been done right at that site.
> ....
> The CRO is doing this, although sometimes the company will commission an independent quality assurance company to do this as well. There were actually a handful of CROs that were working for Helsinn on contract, located in different countries, who were working on the whole execution and assembling of the data.
> ....

> What we see here or what we know about these three trials is that it took about eight weeks. That's most clearly shown in the study report for the 99-03 in which there's a meeting that's identified that happened on December 11th and 12th of 2002 [sic: 2001], in which the data quality committee got together to discuss all of the assembled data.
> ....
> [That] whole process is called blind data review, but the meeting in December, it was sort of the final summit meeting of the independent evaluators who were qualifying the data.

(Dkt. 337 at 65–67.)[33]

Dr. Peck testified that the two-day "blind review" meeting was conducted independent of Helsinn, and Helsinn did not participate in any of the blind data review. (Id. at 67–68.) Dr. Peck said that meeting resulted in a formal protocol amendment submitted to the FDA on December 13, 2001, revising the study groups that would be analyzed for efficacy, as described in the Final Study Report. (Id. at 67–68, 165–66.)

The PALO-99-03 records state that after the "blind review" meeting, the database was closed on December 19, 2001. (DTX-0288-0056.) Dr. Peck referred to that as when the data was "locked." (Dkt. 337 at 66.) Dr. Calderari testified that he did not see any of the blinded data results, and he did not know whether anyone else at Helsinn saw blinded results after the last patient out date of the PALO-99-03 study. (Dkt. 322 at 56–57 (bracketed text added).)

[33] Dr. Peck stated that the PALO-99-03 blind review meeting was on December 11 and 12, 2002, as cited above. The meeting was actually on December 12 and 13, 2001. (See DTX-0288-0056.) He apparently misspoke the date, but the record is clear.

Dr. Peck was asked whether the clinical study data could change during the period immediately after the "last patient out" date. He said:

> [T]he raw data can change during that period of time, yes. Because if they discover a blunder, [if] they discover that the data was not legible, if they find that one of the patients actually got the wrong drug, there's a lot of things that can happen during the data quality evaluation that can lead to changing actually the raw data. It's only after the raw data have been qualified and the database locked, what they call locked -- and that's the point in time where they have decided that, yes, we've done all of the quality control ... that we possibly can and we think this data is valid.

(Dkt. 337 at 66–67.)

The PALO-99-03 documents list January 2, 2002 as the "unblinding" date, which Dr. Peck said was the first date that the sponsor, Helsinn, would have been allowed to see the data. (Id. at 164–65; see DTX-0288-0056.) However, the data was only in preliminary form at that time, and much analysis remained to be done on that one study alone, according to Dr. Peck's explanation quoted in the margin.[34]

Dr. Calderari recalled that the unblinded preliminary data on PALO-99-03 were sent to Helsinn [by the CRO conducting the study] in January, 2002, and that preliminary

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[34] Dr. Peck described the process of analysis that spanned the period from the "unblinding" date to completion of the final study report as follows:

> The moment of unblinding, the data sets are now available for analysis. There's a mountain of data in this clinical trial. 600 -- or 500 and some patients, each patient observed for various values of one sort or another, including vomiting, probably 2 to 300 times. If you count the data items themselves, it's humongous. You don't just push a button and, bingo, there's your full study report ready to go to FDA. It's a very tedious effort. And even along the way, if they have not confirmed that certain assumptions were made with respect to the statistical analyses, they may go back to FDA and talk about . . . an alternative analysis.

(Dkt. 337 at 73–74.)

data "show efficacy for the product." (Dkt. 322 at 61.) He said that was a happy day at the company; "we were start seeing that our effort were paying off, but, of course, we were very careful because they were preliminary data." (Id.)

Helsinn sent a letter to CDER dated February 7, 2002 (the week after the critical date of January 30, 2002), stating in part as follows:

> In accordance with 21 CFR 312.47 (b)(2), a pre-NDA meeting is requested in preparation for the palonosetron NDA. All phase 3 efficacy trials ... have completed enrollment and preliminary efficacy data are available.
>
> Consistent with your letter of October 10, 2001, please find attached at Appendix #1 preliminary efficacy data for PALO-99-03. In this study, the preliminary data for Complete Response, which is the primary efficacy outcome measure for acute CINV, was 81.0% (153/189) for palonosetron 0.25 mg, 73.5% (139/189) for palonosetron 0.75 mg, and 68.6% (127/185) for ondansetron 32 mg. Preliminary efficacy results for PALO-99-04 will be included in the background information package projected to be submitted four weeks prior to the meeting, and preliminary efficacy data for PALO-99-05 will be presented at the meeting.
>
> The following product information is provided to you regarding the suggested meeting:
>
> 1. **Product name and application number**: Palonosetron HCl Intravenous Injection, 0.25 mg (0.05 mg/mL), or 0.75 mg (0.15 mg/mL). Please note that one of these product strengths will be selected for marketing approval based on the phase 3 efficacy data. The NDA number is 21-372.

(DTX-0264-0001.)

The tables of "preliminary efficacy data" attached to that Helsinn letter to the FDA dated February 7, 2002 letter were dated January 7, 2002. (Id. at -0009 to -0011.) Dr. Calderari testified that he could not recall when he first saw the data in those tables, but he would assume that he did see the data before January 15, 2002. (Dkt. 322 at 72.)

Portions of two of those charts are shown in the margin.[35] See n.37 infra and accompanying text.

[35] The tables attached to the February 7, 2002 Helsinn letter to the FDA, described as PALO-99-03 preliminary data, included the following content:

PALO-99-03

TABLE

Summary of Complete Response (Proportions) (n/%)
(Intent-to-treat Cohort)

	Treatment Group		
	Palonosetron 0.25 mg (N=189)	Palonosetron 0.75 mg (N=189)	Ondansetron 32 mg (N=185)
Period			
0 - 24 h	153 (81.0%)	139 (73.5%)	127 (68.6%)
>24 - 48 h	154 (81.5%)	132 (69.8%)	122 (65.9%)
>48 - 72 h	161 (85.2%)	147 (77.8%)	124 (67.0%)
>72 - 96 h	168 (88.9%)	161 (85.2%)	146 (78.9%)
>96 -120 h	175 (92.6%)	169 (89.4%)	161 (87.0%)
>24 -120 h	140 (74.1%)	122 (64.6%)	102 (55.1%)
0 - 48 h	141 (74.6%)	119 (63.0%)	111 (60.0%)
0 - 72 h	137 (72.5%)	116 (61.4%)	97 (52.4%)
0 - 96 h	132 (69.8%)	112 (59.3%)	94 (50.8%)
0 -120 h	131 (69.3%)	111 (58.7%)	93 (50.3%)

N = Number of patients in specific group
n = Number of patients
Calculation of percentages based on N

(DTX-0264-0009.)

PALO-99-03

TABLE

Summary of Complete Response (Confidence Intervals for Group Differences)
(Intent-to-Treat Cohort)

	Difference		
	Palonosetron 0.25 mg - Ondansetron 32 mg (97.5% CI)	Palonosetron 0.75 mg - Ondansetron 32 mg (97.5% CI)	Palonosetron 0.75 mg - Palonosetron 0.25 mg (95% CI)
Period			
0 - 24 h	[1.8%, 22.8%]	[-6.1%, 15.9%]	[-16.4%, 1.5%]
>24 - 48 h	[4.9%, 25.1%]	[-7.6%, 15.2%]	[-20.7%, -2.6%]
>48 - 72 h	[8.0%, 28.4%]	[-0.1%, 21.6%]	[-15.7%, 0.5%]
>72 - 96 h	[1.5%, 19.5%]	[-2.6%, 16.3%]	[-11.0%, 3.6%]
>96 -120 h	[-2.0%, 13.1%]	[-5.6%, 10.4%]	[-9.5%, 3.1%]
>24 -120 h	[7.5%, 30.3%]	[-2.4%, 21.3%]	[-19.3%, 0.3%]
0 - 48 h	[3.3%, 25.9%]	[-8.6%, 14.8%]	[-21.4%, -1.8%]
0 - 72 h	[8.5%, 31.6%]	[-3.0%, 20.8%]	[-21.1%, -1.2%]
0 - 96 h	[7.4%, 30.7%]	[-3.6%, 20.5%]	[-20.7%, -0.5%]
0 -120 h	[7.4%, 30.7%]	[-3.6%, 20.5%]	[-20.7%, -0.4%]

(DTX-0264-0011.)

A further explanation of portions of the PALO-99-03 documents was provided at trial by Teva expert witness Dr. John Fruehauf. He is an M.D. clinical oncologist who also has a Ph.D. in pharmacology. He is a professor of clinical medicine and director of clinical pharmacology and developmental therapeutics at University of California Irvine. He has an active practice at the Chao Family Comprehensive Cancer Center, one of 43 comprehensive cancer centers in the United States. As director of developmental therapeutics, he is regularly involved in conducting Phase I, Phase II, and Phase III clinical trials. (Dkt. 324 at 5–8.)

Dr. Fruehauf and Dr. Peck testified as to their conflicting opinions on whether a person of ordinary skill in the clinical sciences would know, as of January 30, 2002, that palonosetron administered to a human reduces the likelihood of CINV, and specifically whether such person would know at that time that the 0.25 mg dosage claimed in the '219 patent was effective for CINV. (See generally dkt. 324 (Dr. Fruehauf); dkt. 337 (Dr. Peck).) That opinion testimony is discussed in Section II.A.4.b.2.

Testifying about the PALO-99-03 study documents themselves, Dr. Fruehauf stated that it was not surprising to see that the database was "unblinded" on January 2, 2002, and the three summary tables attached to Helsinn's February 7, 2002 letter to the FDA were dated January 7, 2002, less than a week after the data was unblinded. He pointed out that those tables, which do include some statistical analysis, are indicated at the bottom of each page to have been prepared using SAS. (Dkt. 324 at 61–63.)

Dr. Fruehauf explained that SAS is a widely accepted statistical package that was included in the pre-planned protocol for that Phase III study, "so before anybody went on this study, it was determined that this is what they would do." (Id. at 61.) On the other hand, referring to the later PALO-99-04 locked data, he did acknowledge that before the final reports of these Phase III studies were completed, "there were other things, statistics and other things that might be done" to analyze the locked data of those studies. (Id. at 204.)

Dr. Calderari, as head of the Helsinn palonosetron development program but not himself a clinician, was asked whether, upon receipt of that data in early 2002, he formed any conclusion as to whether palonosetron would definitely work for the reduction of CINV. He said no; "that was an indication that the first preliminary data set was positive; but ... we, as part of the overall plan, we have to have two pivotal trials to be completed successfully in order to show efficacy of the product, so 99-03 and 99-04." (Dkt. 322 at 137–38.) When asked whether this data gave him confidence that both of those trials would successfully show efficacy, he replied, "[n]o, because unfortunately, as we know very well, drug development, ... one trial is independent from the other one. You are also using different investigator, different countries, different populations, so there might be difference between two trials." (Id. at 138.)

Helsinn, together with its U.S. licensee and selected marketing partner MGI Pharma, issued a press release on January 16, 2002. The text of that announcement is quoted in full in the margin.[36]

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[36] The January 16, 2002 press release stated:

> HELSINN HEALTHCARE SA, a privately owned Swiss pharmaceutical group, and MGI PHARMA, INC., (Nasdaq: MOGN) an oncology-focused pharmaceutical company based in Minneapolis, today announced that patient treatment is completed and the data analysis is underway for the pivotal Phase 3 trials of their investigational agent, Palonosetron. **Palonosetron** is a potent, highly selective 5-HT3-receptor antagonist in development in North America and Europe for the prevention of chemotherapy-induced nausea and vomiting (CINV). Submission of the New Drug Application (NDA) for Palonosetron is now planned to occur in the third quarter of 2002.
>
> The Phase 3 clinical trial program was initiated in April 2000 and was designed to compare intravenous (IV) Palonosetron to currently marketed 5-HT3 antagonists. The trials were conducted at more than 130 medical centers across North America and Europe, with more than 1,800 cancer patients receiving either highly- or moderately-emetogenic chemotherapy. Based on the extended half-life of Palonosetron and the results of a Phase 2 trial, the efficacy of Palonosetron in the Phase 3 trial is being assessed over Day 2 though Day 5 following treatment, in addition to the primary efficacy measure of complete response during the 24-hour period after the start of chemotherapy.
>
> "**We are pleased to have completed all patient treatment and to have begun analysis of the data collected in the Palonosetron Phase 3 clinical program**," said Luigi Baroni, senior director of Scientific Affairs Division at HELSINN. "**The Phase 2 clinical trial results were promising, and we are hopeful that the Phase 3 Palonosetron data will demonstrate that it can make a difference for cancer patients suffering from CINV**."
>
> "**The half-life of other available 5-HT3 receptor antagonists ranges from approximately five to nine hours, where Palonosetron has a plasma elimination half-life of nearly 40 hours**,", notes Dr. John MacDonald, senior vice president of Research and Development at MGI. "**The activity seen with Palonosetron in the Phase 2 trial, coupled with its safety profile observed to date, led to the initiation of a Phase 3 program to assess the ability of the drug to provide prolonged protection against CINV with a single dose**."

(DTX-0040-0001 (emphasis in original).)

11. Status as of patent application date, January 30, 2003

This section describes the chronology of the further palonosetron drug development events between the critical date of January 30, 2002, and the January 30, 2003 provisional application date of all four patents-in-suit.

It will be recalled that each of the three full-scale Phase III studies had reached the "last patient out" date in the fourth quarter of 2001. The clinical data from the earliest-completed study, PALO-99-03, had been "locked" on December 19, 2001, and had been "unblinded" and therefore available to be viewed by Helsinn on January 2, 2002. See Section I.C.10. The database of PALO-99-04 was locked on February 22, 2002 and that data was unblinded on February 28, 2002. (DTX-0289-0054.) The "locked" date for PALO-99-05 was March 14, 2002, and that data was unblinded on March 19, 2002. (DTX-0290-0023.)

The letter from Helsinn to the FDA, although dated and sent on February 7, 2002, has been described above as falling within the January 30, 2002 critical date period, because the tables of PALO-99-03 preliminary data attached to that letter were prepared and known to Helsinn before January 30, 2002. See Section I.C.10. Presumably that requested meeting with the FDA to review preliminary results of PALO-99-03, as well as preliminary results of PALO-99-04 and PALO-99-05 when available, did take place at a date not specified in the evidence.

The final reports on those three studies were named Clinical Study Reports. Those Reports for PALO-99-03 and for PALO-00-04 were each dated July 19, 2002. (DTX-

0288-0003; DTX-0289-0002.) The Clinical Study Report for PALO-00-05 was dated August 2, 2002. (DTX-0290-0002.) The Analysis Report of the re-analysis of Phase II study 2330 data, entitled "Fixed Dose Conversion and Historical Placebo Control Post-Hoc Efficacy Analysis (code PALO-00-01)," was dated August 8, 2002. (PTX-182.0003.)

The Clinical Study Report for PALO-99-03 was 250 pages long, exclusive of appendices. That report, with appendices, occupied 17 volumes in the subsequent NDA filing. (See DTX-0288-0003 and -0013 to -0018.) The Clinical Study Reports and appendices for PALO-99-04 and PALO-99-05 were comparable documents. (See DTX-0289 and DTX-0290.)

The Conclusion in the Synopsis section of the PALO-99-03 Clinical Study Report stated:

> In this study, non-inferiority of the 2 doses of palonosetron (0.25 mg and 0.75 mg) to ondansetron 32 mg was demonstrated for the complete response rate during the first 24 hours after chemotherapy, the primary efficacy parameter. Furthermore, non-inferiority of both palonosetron groups compared to ondansetron was also shown for most secondary efficacy parameters and palonosetron 0.25 mg was shown to be superior to ondansetron with regard to most of these secondary efficacy parameters. Thus, palonosetron 0.25 mg showed a better efficacy profile over ondansetron during the delayed phase of nausea and vomiting. The rate of patients with adverse events was comparable in the treatment groups and showed a similar pattern. There were no safety concerns associated with results of laboratory parameters, vital signs and ECG recordings and Holter monitoring measured during the study.

(DTX-0288-0012.) The corresponding Conclusion sections of the PALO-99-04 and PALO-99-05 Clinical Study Reports contained similar types of information. (See DTX-0289-0012; DTX-0290-0011.)

The Synopsis section of the PALO-99-03 Clinical Study Report also contained exactly the same efficacy summary numbers that had been communicated to the FDA in the preliminary data tables attached to Helsinn's letter dated February 7, 2002. See n.35 supra. Those numbers were set forth in Table 1 and Table 2 of the Synopsis, as also contained in the appendix materials submitted with that Report. (See DTX-0288-0009 and -0095.) Those two tables are shown in the margin.[37]

[37] The tables shown under "Efficacy results" in the Summary portion of the Synopsis section of the PALO-99-03 Clinical Study Report were as follows:

Synopsis continued

Name of Sponsor/Company: **Helsinn Healthcare SA**	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: Palonosetron HCl	Page:	

Statistical methods (continued): Differences between the treatment groups regarding time to first emetic episode, time to first administration of rescue medication and time to treatment failure were analyzed using Kaplan-Meier estimates and a Log-Rank test.
Incidences for adverse events were calculated overall, by category, by body system and by preferred term. In addition, 95% CI were provided for the overall incidence and for the incidence by category of adverse events in each treatment group. Changes in laboratory values with respect to toxicity grades were investigated for each time point within each group using Wilcoxon matched pairs signed rank test. All other safety parameters were analyzed descriptively.

Summary

Efficacy results:

The proportion of patients who achieved a complete response and the results from the statistical analysis of the primary efficacy parameter complete response rate during the first 24 hours after chemotherapy are displayed in Table 1, whereas in Table 2 the 97.5% CIs of the difference in CR rate of each dose of palonosetron versus ondansetron are depicted.

Table 1: Patients with a complete response rates during the first 24 hours after chemotherapy (ITT cohort, N = 563)

Time period (hours)	Palonosetron 0.25 mg (N = 189)		Palonosetron 0.75 mg (N = 189)		Ondansetron 32 mg (N = 185)	
	N	%	N	%	N	%
0-24	153	81.0	139	73.5	127	68.6

Table 2: The 97.5% confidence interval for the difference in complete response rates during the first 24 hours after chemotherapy between the palonosetron groups and the ondansetron group (ITT cohort, N = 563)

	Palonosetron 0.25 mg minus ondansetron 32 mg	Palonosetron 0.75 mg minus ondansetron 32 mg
97.5% CI	[1.8%; 22.8%]	[-6.1%, 15.9%]

The lower limit of the 97.5% confidence interval for the difference in complete response rates during the first 24 hours after chemotherapy was above –15% (pre-set threshold) for both comparisons of palonosetron to ondansetron 32 mg. Therefore, the non-inferiority of both palonosetron doses to ondansetron 32 mg was demonstrated for the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting. Furthermore, the lower limit of the 97.5% confidence interval of the comparison palonosetron 0.25 mg with ondansetron was above zero, indicating superior complete response rates in the palonosetron 0.25 mg group compared to the ondansetron group. The results from the PP cohort were consistent with the ITT analysis.

(DTX-0288-0009.)

The detailed contents of the PALO-99-03 Clinical Study Report, following the Synopsis, included a narrative headed Additional changes after unblinding. Portions of that section are also quoted in the margin.[38]

[38] That portion of the PALO-99-03 Clinical Study Report stated in part as follows:

- Additional statistical analyses.

  An additional statistical analysis was performed for the number of emetic episodes, which presented the number of patients with 0, 1, 2 and ≥3 emetic episodes for each time interval. Furthermore, quartiles were calculated for quality of life, time to first emetic episode, time to treatment failure, time to the first administration of rescue medication and patients global satisfaction because median, mean, minimum and maximum values did not show the differences between the treatment groups, which were seen by statistical testing. Further additional analyses were performed on dosage and time of infusion of chemotherapy given on Day 1.
  ....

- Change in the statistical analysis.

  The normal distribution of data (number of emetic episodes, patient global satisfaction, quality of life) was to be assessed by the Shapiro-Wilk test before the application of parametric tests. However, the non-normality was obvious form [sic: from] the summary tables. Therefore, the Shapiro-Wilk test was omitted and a non-parametric method was used.
  ....

- Trial validation.

  A new formula for the trial validation was developed because a mistake was detected in the database. Moreover, additional information regarding the percentage of patients in each study treatment arm using concomitant steroids was added. It was decided to consider both formulas (original and updated formulas) for the validation of study PALO-99-03.

(DTX-0288-0071, -0072 (bracketed text added).)

Helsinn filed its New Drug Application, NDA 21-372, on September 27, 2002, approximately one month after the above-listed clinical reports were completed. (See PTX-121.) All of those reports, as well as voluminous other data, were included in that NDA filing. (See NDA number 21-372 on each title page of above-cited report exhibits.) Helsinn sent additional submissions to the FDA dated October 11 and November 21, 2002, January 24, April 9, April 24, May 15, June 9, June 13, June 18, June 20, June 25, July 1, July 17, and July 22, 2003. (See PTX-121.)

Helsinn made at least one publication of some of its unblinded Phase III data during the period between January 30, 2002 and the patent application date of January 30, 2003. That was an oral presentation accompanied by an abstract, authored by Helsinn's Dr. Macciocchi and research colleagues Steven M. Grunberg et al., described as "for the PALO-99-04 Study Group." ("the Grunberg abstract"). It was entitled "Palonosetron is active in preventing acute and delayed emesis following moderately emetogenic chemotherapy: Results of a phase III trial." (PTX-297.0002.)

The Grunberg abstract was presented at the June 23–26, 2002 conference of the Multinational Association of Supportive Care in Cancer in Boston. (PTX-297.0001.) At that time, the PALO-99-04 data had been unblinded and under analysis since February 28, 2002, and the final Clinical Study Report would be completed and dated July 19, 2002. Also, of course, the data of the companion study, PALO-99-03, had been unblinded and under analysis since January 2, 2002, and its Clinical Study Report would also be dated July 19, 2002. See Section I.C.11.

There was text and a table in the one-page Grunberg abstract. The table showed efficacy results of Helsinn's 0.25 mg. and 0.75 mg palonosetron dose levels in comparison with dolasetron, for acute and delayed CINV in moderately emetogenic chemotherapy, as the PALO-99-04 trials had studied. The Conclusion stated in the Grunberg abstract was: "Palonosetron has demonstrated significant activity in preventing both acute and delayed emesis with a single I.V. dose in patients receiving moderately emetogenic chemotherapy. Palonosetron was safe and well tolerated." (PTX-297.0002.)

Helsinn filed Provisional Patent Application No. 60/444,351 at the U.S. Patent and Trademark Office on January 30, 2003. (See dkt. 289 (patent family history chart).) On that date, Helsinn's New Drug Application 21-372 was still pending at the FDA.[39]

12. Issuance of patents-in-suit

The procedural history of the prosecution of the patents-in-suit, subsequent to the filing date of the provisional application on January 30, 2003, has been summarized in

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[39] FDA approval of Helsinn's NDA 21-372 was issued on July 25, 2003. The approval letter stated in pertinent part:

> This new drug application provides for the use of Aloxi® (palonosetron hydrochloride injection) for:
> 1) the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and
> 2) the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderate emetogenic cancer chemotherapy.
>
> We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

(PTX-121.0001, -.0015.)

this Court's claim construction Memorandum Opinion filed in this case on April 22, 2015. (See dkt. 290 at 16–18.) Here we briefly summarize the basic chronology of those prosecution events, omitting record citations that are stated in that earlier Opinion.

The first generation of patents to be issued subsequent to the January 30, 2003 provisional application date were the '724 and '725 patents-in-suit, dated May 24, 2011. Thus, the original prosecution for this patent family took approximately 8½ years. The next patent-in suit, the '424 patent, was issued on June 14, 2011.

The '724, '725, and '424 patents, all sharing a contemporaneous prosecution era, were approved only after appeals in all three cases to the Commissioner of Patents. Much file history was accumulated in those prosecution files.

The '219 patent, with the same provisional application date and an actual filed application date of May 23, 2013, was issued on December 3, 2013. That patent was applied for and granted during the pendency of this litigation. The application history of the '219 patent itself, albeit not as extensive as for the other three patents, includes many of the materials filed in this litigation including expert reports. (See '219 patent, pages 1–6.) The other patents issued to date in this patent family tree, and abandoned applications, are listed in the chart supplied by the parties. (Dkt. 289.)

13. Claim construction rulings regarding prosecution history

This Court has issued claim construction opinions interpreting some claim limitations of the patents-in-suit pertaining to both the stability and the efficacy aspects of

the claims. Those opinions were filed during claim construction proceedings in this case and in a related case, Civil Action No. 12-2867.

The claim construction Memorandum Opinion filed in this case, on April 22, 2015, addressed the issue of whether the following portion of the preamble of claim 1 of the '219 patent constitutes claim limitation language: "for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting." This Court ruled that language to be limiting in its entirety. (Dkt. 290.) The discussion in that opinion included a review of portions of the prosecution history of all of the patents-in-suit, as it was recognized that the earlier patent histories can be relevant to interpreting the claims of later-issued patents in the same family.

That opinion described, inter alia, a phase early in the prosecution of the '724, '725, and '424 patents when the examiners rejected the term "preventing emesis" in applied-for preambles to each of those patents under 35 U.S.C. § 112 (enablement). (See dkt. 290 at 20.) The applicants overcame that ground for rejection in each of those applications by substituting the words "for reducing emesis or reducing the likelihood of emesis." (Id.)

To overcome that ground for rejection, the applicants successfully argued as follows, in a telephone interview with the examiners quoted from here in the file history of the '424 patent:

> During the telephone interview, a proposed amendment to the claims in the '270 application was discussed. Applicant understood the Examiner's primary concern with the claims to be with the word "preventing," recited

> in independent claims 1 and 11 of the '270 application. Applicant indicated that palonosetron has been approved by the Food and Drug Administration for preventing emesis, and is marketed as a drug for preventing emesis.
>
> The Examiners suggested that an amendment to independent Claims 1 and 11 in the '270 application, wherein Applicant includes the phrase "reducing the likelihood" of emesis instead of "preventing" emesis, would address the Office's concerns. Applicant has amended the claims in this application in accordance with the Examiners' suggestions for the '270 application.

(Dkt. 178-3 at 116 (Examiners' Summary of July 27, 2006 Telephonic Interview).)

This portion of the common prosecution history of the patents-in-suit may be relevant to the on-sale bar issues in this case, discussed in Section II.A.4.

14. ANDA filings by Teva and others

Teva's Abbreviated New Drug Application ("ANDA") seeks approval for a generic Aloxi® product that can have one of two dosage strengths: (1) a 0.25 mg/5 ml dosage strength, used to prevent chemotherapy-induced nausea and vomiting ("the CINV dosage strength"); and (2) a 0.075 mg/1.5 ml dosage strength, used to prevent postoperative nausea and vomiting ("the PONV dosage strength"). (See dkt. 207 at 4.) The concentration of both proposed Teva products is 0.05 mg/mL, because the 0.25 mg dose solution is 5 ml and the 0.075 mg dose solution is 1.5 ml.

II. CONCLUSIONS OF LAW[40]

A. On-sale bar

The Court will now turn to the issue of the on-sale bar and its application to this case. "[T]he patent system represents a carefully crafted bargain that encourages both the creation and the public disclosure of new and useful advances in technology, in return for an exclusive monopoly for a limited period of time." Pfaff v. Wells Elec., Inc., 525 U.S. 55, 63 (1998). Before 2011, Section 102 of the Patent Act balanced this "carefully crafted bargain" by providing that:

> A person shall be entitled to a patent unless . . . (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States . . . .

35 U.S.C. § 102, amended by Leahy-Smith America Invents Act, Pub.L. No. 112-29, 125 Stat. 254 (2011) (emphasis added) ("AIA"). This provision, referred to as the on-sale bar, serves as a bar to patentability if the claimed invention is (1) made the "subject of a commercial offer for sale," and (2) the invention is "ready for patenting." See Pfaff, 525 U.S. at 67. A sale under this bar occurs when the parties offer or agree to reach a contract "to give and pass rights of property for consideration which the buyer pays or promises to pay the seller for the thing bought or sold." Zacharin v. United States, 213 F.3d 1366, 1370 (Fed.Cir. 2000) (quotation and citation omitted).

[40] To the extent that the "Conclusions of Law" portion of this opinion contains findings of fact in addition to those expressly set out under the heading "Findings of Fact," they shall be deemed to be part of the findings of fact.

1. Legal standards and post-AIA statutory construction

a. Historical analysis

Historically, a secret sale or offer for sale of a claimed invention has precluded patentability under the on-sale bar. See Metallizing Eng'g Co. v. Kenyon Bearing & Auto Parts Co., 153 F.2d 516, 520 (2d Cir. 1946) (Hand, J.) ("[I]t is a condition upon an inventor's right to a patent that he shall not exploit his discovery competitively after it is ready for patenting; he must content himself with either secrecy, or legal monopoly."); Egbert v. Lippman, 104 U.S. 333 (1881). The invention at issue in Egbert, a corset improvement, was given by the inventor to a woman who wore the corset under her dress, rendering it unobservable to the general public. See Egbert, 104 U.S. at 337. The Supreme Court found that the inventor's corset improvement was in public use, noting that "[i]f an inventor, having made his device, gives or sells it to another . . . without limitation or restriction, or injunction of secrecy, and it is so used, such use is public, even though the use and knowledge of the use may be confined to one person." See id.[41]

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[41] The Court notes that pre-AIA § 102 language also included a public use bar. See 35 U.S.C. § 102, amended by § 102(a)(1), 125 Stat. at 285–86 ("A person shall be entitled to a patent unless . . . (b) the invention was . . . in public use . . . ."). As a historical note, the public use and on-sale bars were often not differentiated by courts, or were referred to using other terminology. See, e.g., Metallizing Eng'g Co., 153 F.2d at 520 (borrowing statutory language from Patent Act of 1839 and referring to on-sale and public use bars as "prior use"). The relationship between the § 102 bars was explained by the Supreme Court in Pfaff:

> We originally held that an inventor loses his right to a patent if he puts his invention into public use before filing a patent application. His voluntary act or acquiescence in the public sale and use is an abandonment of his right. A similar reluctance to allow an inventor to remove existing knowledge from public use undergirds the on-sale bar.

Pfaff, 525 U.S. at 64 (quoting Pennock v. Dialogue, 27 U.S. 1, 2 (1829) (Story, J.)).

The legal principle set forth in Egbert—that a claimed invention given or sold to one individual or entity in secrecy can constitute a public use—has proliferated a line of precedent in which secret sales or offers for sale bar patentability. See, e.g., Special Devices, Inc. v. OEA, Inc., 270 F.3d 1353, 1357–58 (Fed.Cir. 2001) (finding that on-sale bar invalidated patent, although contract for sales of invention was only for purpose of commercial stockpiling by supplier and sales were confidential); Woodland Trust v. Flowertree Nursery, Inc., 148 F.3d 1368, 1370 (Fed.Cir. 1998) ("Thus an inventor's own prior commercial use, albeit kept secret, may constitute a public use or sale under § 102(b), barring him from obtaining a patent."); Hall v. Macneale, 107 U.S. 90, 96 (1883) (finding that an inventor's "burglar-proof" safes were in public use after inventor sold three safes, despite testimony that technology was completely concealed within safe).

On September 16, 2011, the AIA was signed into law with the objective of "establish[ing] a more efficient and streamlined patent system that will improve patent quality and limit unnecessary and counterproductive litigation costs." (Dkt. 236-3 at 81 (AIA Committee Report).) The AIA's most significant change was the conversion of the United States' patent system from a "first-to-invent" to a "first-inventor-to-file" system, which now "encourages the prompt filing of patent applications" and redefines the effective filing date as the date of the patent application, rather than the date of the invention. See 35 U.S.C. § 100(i)(1)(A) (1-24-2008 Committee Report).[42]

[42] As will be discussed later, Plaintiffs argue that this overall change to the patent system also supports a new interpretation of the on-sale bar.

In converting to a first-inventor-to-file system, Congress attempted to modernize and streamline many facets of the patent system, including the identification of prior art. (See dkt. 236-3 at 83–84 (AIA Committee Report) ("Prior art will be measured from the filing date of the application and will typically include all art that publicly exists prior to the filing date, other than disclosures by the inventor within 1 year of filing.").) As discussed above, the on-sale bar analysis under the Egbert rationale had led to unusual or extreme results for patentees who sought to obtain a patent after such secret use or sales. (See id. at 17 (statement of Senator Kyl in Mar. 8, 2011 Congressional Record, in which he describes effect of on-sale bar and public use bar as "impos[ing] extreme results to no real purpose.").)

The AIA thus redefined the scope of prior art under § 102 as follows:

> A person shall be entitled to a patent unless—(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention . . . .

35 U.S.C. § 102(a)(1).

The AIA added the clause "otherwise available to the public," and also regrouped the categories of prior art under § 102. Compare 35 U.S.C. § 102, amended by § 102(a)(1), 125 Stat. at 285–86 (designating prior art categories as follows: "patented or described in a printed publication in this or a foreign country or in public use or on sale in this country. . . ."), with 35 U.S.C. § 102(a)(1) (designating prior art categories as:

"patented, described in a printed publication, or in public use, on sale, or otherwise available to the public. . . .").

b. Parties' arguments regarding on-sale bar

It is against this historical and statutory background that this Court decides whether § 102(a)(1) of the AIA requires a sale or offer for sale of a claimed invention to be "available to the public before the effective filing date" of the claimed invention in order for the on-sale bar to apply and possibly invalidate a patent. (See generally dkt. 204; dkt. 209; dkt. 226; dkt. 236.)[43]

Plaintiffs argue, as a threshold matter, that the '219 patent is subject to the AIA. (See dkt. 209 at 18–19.) The AIA states in pertinent part:

> [T]he amendments made by this section shall take effect upon the expiration of the 18–month period beginning on the date of the enactment of this Act [September 16, 2011], and shall apply to any application for patent, and to any patent issuing thereon . . . .

35 U.S.C. § 3(n).

Plaintiffs additionally argue that the AIA established a new standard for the on-sale bar, i.e., that commercial sales or offers for sale of the invention must now be made available to the public for the on-sale bar to apply. (See dkt. 209 at 7.) Plaintiffs argue that the contracts with service providers Oread, Inc. ("Oread") and SP Pharmaceuticals

[43] Defendant, in its opposition to Plaintiffs' motion for partial summary judgment, relied in part on Sandoz's motion for summary judgment of invalidity of the '219 patent under the on-sale bar. (See dkt. 226 at 8, n.1.) Sandoz's motion for summary judgment was terminated by way of a consent judgment but will be cited to in this Memorandum Opinion insofar as Defendant incorporated these arguments into this motion. (See dkt. 247.)

L.L.C. ("SP"), and the licensing and supply agreements with MGI Pharma, Inc. ("MGI") were not commercial sales or offers for sale. (See id.) Plaintiffs argue in the alternative that even if this Court considers these contracts to be commercial sales or offers for sale, the post-AIA on-sale bar applicable to the '219 patent does not apply because the contracts never made the invention available to the public. (See id.)

Teva argues that the AIA did not amend the on-sale bar to include a public sale requirement. (See dkt. 226 at 9.) Teva asserts that under the correct interpretation of the AIA, Helsinn violated the on-sale bar by executing a supply agreement for the marketing and sale of Aloxi with MGI. (See id. at 10.) Teva additionally argues that Helsinn violated the on-sale bar even under Helsinn's proposed interpretation of the AIA, as the supply agreement was publicized and MGI is a member of the public. (See id.)

c. Interpreting the legal standard

1. Statutory construction

The Court's first inquiry in interpreting a statute "is to determine whether the language at issue has a plain and unambiguous meaning with regard to the particular dispute in the case. Our inquiry must cease if the statutory language is unambiguous and the statutory scheme is coherent and consistent." Bettcher Indus., Inc. v. Bunzi, USA, Inc., 661 F.3d 629, 644 (Fed.Cir. 2011) (quotation and citation omitted).

The parties in this case dispute whether the last clause of § 102(a)(1), "otherwise available to the public," modifies the section's previous clauses or serves as its own category of prior art. (See dkt. 209 at 21 ("Since the modifier 'or otherwise available to

the public' in § 102(a)(1) is a catchall phrase, it applies to each preceding category of prior art in that section that must make the claimed invention available to the public, including an alleged 'sale.'"); but see dkt. 226 at 20 ("[T]he phrase 'or otherwise available to the public' creates a residual category of prior art to capture invalidating disclosures that do not fall into one of the enumerated categories in section 102.").)

This Court is guided by the Supreme Court's "common sense" approach to statutory interpretation. See Paroline v. United States, 134 S.Ct. 1710, 1721 (2014) ("Reading the statute to impose a general proximate-cause limitation accords with common sense.").[44] The statute at issue in Paroline included six categories of covered losses and a final clause that covered "any other losses suffered by the victim as a proximate result of the offense." See id. at 1720. The victim argued that the proximate causation requirement only applied to the final "catchall" category in the statute. See id. at 1720–21. The Court disagreed, holding that "[w]hen several words are followed by a clause which is applicable as much to the first and other words as to the last, the natural construction of the language demands that the clause be read as applicable to all." Id. at 1721 (quotation and citation omitted).

The Paroline court further noted that "[i]t is . . . a familiar canon of statutory construction that [catchall] clauses are to be read as bringing within a statute categories

[44] The Supreme Court references the surplusage canon of statutory construction, which provides that "[i]f possible, every word and every provision is to be given effect . . . . None should be ignored. None should needlessly be given an interpretation that causes it to duplicate another provision or to have no consequence." ANTONIN SCALIA & BRYAN A. GARNER, READING LAW: THE INTERPRETATION OF LEGAL TEXTS 174 (1st ed. 2012). Justice Scalia noted that this truism applies to "all sensible writing." See id.

similar in type to those specifically enumerated." Id. This "familiar canon of statutory construction," the associated-words canon, arises when words "are associated in a context suggesting that the words have something in common." SCALIA & GARNER, supra note 44, at 195. These associated words often "involve listings," but a list is by no means a prerequisite. See id. at 197. When applying the associated-words canon, "[the words] should be assigned a permissible meaning that makes them similar." Id. at 195.

A court must begin with "the assumption that the ordinary meaning of the language chosen by Congress accurately expresses the legislative purpose." See Microsoft Corp. v. i4i Ltd. P'ship, 131 S.Ct. 2238, 2245 (2011) (internal quotation and citation omitted). The use of a term of art, or a "common-law term," generally carries with it the assumption that "the term . . . comes with a common law meaning, absent anything pointing another way." See id. In addition, "when Congress employs a term of art, it presumably knows and adopts the cluster of ideas that were attached to each borrowed word in the body of learning from which it is taken." Air Wisc. Airlines Corp. v. Hoeper, 134 S.Ct. 852, 861–62 (2014). This inquiry will require, as discussed below, a review of a statute's legislative history and the "body of learning" from which the words originated. See id. at 862.

2. Agency guidelines

In the context of patent law, guidelines published by the United States Patent and Trademark Office ("USPTO") are also instructive in interpreting a statute as they provide a practitioner's perspective on a given issue. See, e.g., Examination Guidelines for

Implementing the First Inventor to File Provisions of the Leahy-Smith America Invents Act, 78 Fed. Reg. 11,059, 11,075 (Feb. 14, 2013) (to be codified at 37 C.F.R. 1). While the USPTO guidelines typically serve as a "guide to patent attorneys and patent examiners on procedural matters," a court may take judicial notice of guidelines so long as the USPTO's interpretation does not conflict with the statute. See Molins PLC v. Textron, Inc., 48 F.3d 1172, 1180 n.10 (Fed.Cir. 1995). It should be noted, however, that these guidelines are not binding on a court. See Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964 (Fed.Cir. 2002).

3. Legislative history

This Court must give effect to congressional intent by "look[ing] not only to the particular statutory language, but to the design of the statute as a whole and to its object and policy." Crandon v. United States, 494 U.S. 152, 158 (1990) (citation omitted). Committee Reports, "which represent the considered and collective understanding" of Congress "in drafting and studying proposed legislation," are crucial when considering an issue of first impression. In re Swanson, 540 F.3d 1368, 1376 (Fed.Cir. 2008) (quotation and citation omitted). Although the Supreme Court has identified the Committee Report as the authoritative source on discerning legislative intent, House and Senate records are also instructive in determining a statute's underlying policy. See Bettcher Indus., 661 F.3d at 646 (using relevant House and Senate records to "confirm" interpretation of § 317 of Patent Act).

Prior versions of statutory provisions may also supply further evidence of congressional intent. See Russello v. United States, 464 U.S. 16, 23 (1983). In Russello, the Supreme Court

interpreted a section of the RICO chapter of the Organized Crime Control Act of 1970 by applying the "ordinary meaning of the words used." See id. at 21 (quotation and citation omitted). The Court's interpretation was bolstered by earlier proposed versions of the legislation, which contained a limiting definition of the word at issue. See id. at 23–24. The Court held that "[w]here Congress includes limiting language in an earlier version of a bill but deletes it prior to enactment, it may be presumed that the limitation was not intended." Id. This principle does not only apply to prior limiting language. When looking to prior versions of legislation, courts should "not assume that Congress intended to enact statutory language that it has earlier discarded in favor of other language." See Chickasaw Nation v. United States, 534 U.S. 84, 93 (2001) (internal quotation and citation omitted).

4. Public policy considerations

The last factor that this Court will consider in interpreting § 102(a)(1) is the public policy underlying the passage of the AIA in its entirety. "[T]he meaning of statutory language, plain or not, depends on context." Holloway v. United States, 526 U.S. 1, 7 (1999). Thus, it is essential to consider the AIA's other amendments and Congress's policy goals in enacting them, as these changes illustrate the overarching statutory scheme. See Bettcher Indus., 661 F.3d at 644 ("It is a fundamental canon of statutory construction that the words of a statute must be read in their context and with a view to their place in the overall statutory scheme."). The importance of interpreting a statute in the context of the larger statutory scheme is crucial, as "Congress . . . does not alter the fundamental details of a regulatory scheme in vague terms or ancillary

provisions—it does not, one might say, hide elephants in mouseholes." Whitman v. Am. Trucking Ass'ns, 531 U.S. 457, 468 (2001).

d. Application of legal standards

The Court will now consider the parties' specific arguments regarding their proposed interpretation of § 102(a)(1) of the AIA.

1. Statutory construction

Plaintiffs assert that the plain language of § 102(a)(1) supports their interpretation that a patent may only be invalidated under the AIA's on-sale bar if the claimed invention was made available to the public prior to its effective filing date. (See dkt. 209 at 19.) They argue that the phrase "otherwise available to the public" is a modifying clause that is "applicable as much to the first and other words as to the last." (See id. at 21 (quotation omitted).)

The United States Court of Appeals for the Federal Circuit ("Federal Circuit"), Plaintiffs claim, has endorsed the same interpretation of modifying clauses. (See id.) In Resource Conservation Group, LLC v. United States, 597 F.3d 1238 (Fed.Cir. 2010), the Federal Circuit held that the theory of last antecedent—wherein qualifying words refer solely to the last antecedent—is "overcome by other factors showing a different meaning." See Res. Conservation Grp., LLC, 597 F.3d at 1245. In Finisar Corp. v. DirecTV Grp., Inc., 523 F.3d 1323 (Fed.Cir. 2008), the Federal Circuit held that "when a modifier is set off from a series of antecedents by a comma, the modifier should be read to apply to each of those antecedents." See Finisar Corp., 1523 F.3d at 1336–37. Plaintiffs argue that the placement of the modifying clause "otherwise available to the public," bolstered by the Supreme Court and Federal Circuit

interpretations of similar clauses, renders the statute's language unambiguous. (See dkt. 209 at 20.)

Defendant sets forth two statutory interpretation arguments in opposition to Plaintiffs: (1) the term "on sale" is a term of art that was left unchanged in the AIA and thus the prior meaning still applies; and (2) "otherwise available to the public" is a disjunctive phrase that is meant to serve as a residual category of publicly available prior art. (See dkt. 226 at 18–21.)

Defendant first argues that "when Congress employs a term of art, it presumably knows and adopts the cluster of ideas that were attached to each borrowed word in the body of learning from which it is taken." (See id. at 19 (quotation and citation omitted).) Teva provides the example of the phrase "a patent shall be presumed valid," which the Supreme Court held as requiring a clear and convincing evidence standard. (See id.) See also Microsoft Corp., 131 S.Ct. at 2246. The Supreme Court reasoned that the clear and convincing evidence standard applies "because courts before 1952 had interpreted the presumption in that manner." (See dkt. 226 at 19.) See also In re Nuijten, 500 F.3d 1346, 1356 n.5 (Fed.Cir. 2007) (concluding that by reenacting "manufacture" as a category of patentable subject matter in 1952, despite other changes to 35 U.S.C. § 101, Congress intended to adopt pre-1952 judicial definitions of the term "manufacture"). Defendant argues that Plaintiffs have not "overcome this presumption." (See dkt. 226 at 20; cf. dkt. 204 at 29 ("If Congress had intended to graft a new 'public' requirement onto the on-sale

bar, it could have done so explicitly by adding a 'public' modifier to 'on sale' . . . just as section 102 contains the phrases 'printed publication' and 'public use.'").)

Teva also claims that "otherwise available to the public" constitutes a residual category "to capture invalidating disclosures that do not fall into one of the enumerated categories in section 102." (See dkt. 226 at 20.) Defendant distinguishes Paroline and Resource Conservation by noting that "[n]othing in Paroline—or in Resource Conservation for that matter—suggests that the addition of a catch-all category to a pre-existing statute could change the established meaning of language retained in the statute." (See id. at 21 (emphasis in original).) Teva also highlights Plaintiffs' failure to cite to any case "where an amendment to include a residual 'or otherwise' clause had the effect of deleting decades of precedent. . . ." (Id.)

Plaintiffs flatly disagree with Defendant's argument that "Congress has left the . . . language [of § 102] virtually unchanged from the original 1836 Act." (See dkt. 226 at 19.) Plaintiffs first point out that "the language surrounding the words 'on sale' did change significantly under the AIA." (See dkt. 236 at 9.) Plaintiffs note that the elimination of geographic limitations, the regrouping of different prior art categories, and the addition of "otherwise available to the public" indicate that § 102(a) was not left "virtually unchanged." (See id.) Plaintiffs add that the Defendant's cases discussing an unchanged words presumption are distinguishable because Congress, in those cases, "amended the statutes to include terms of art." (See id. at 9 n.3.) Here, Plaintiffs assert,

Congress "changed the surrounding language in providing a new legal standard, which it elucidated in the legislative history." (Id. at 9.)

Plaintiffs also argue that the Defendant's argument for a residual category that "has no bearing on the scope of the separate 'on sale' category" requires that the word "otherwise" be interpreted as surplusage, which would violate the surplusage canon of statutory interpretation. (See id. at 8.) See also SCALIA & GARNER, supra note 44, at 174.

2. Agency guidelines

Plaintiffs bolster their statutory interpretation argument by referencing the USPTO's published guidelines on § 102(a). (See dkt. 209 at 20.) Plaintiffs note that the USPTO published guidelines after a comment period and its own statutory interpretation analysis, and concluded that "secret sale or use activity does not qualify as prior art." (See id.) The guidelines define a sale or offer for sale as secret "if, for example, it is among individuals having an obligation of confidentiality to the inventor." (Id. at n.10 (quotation and citation omitted).) Plaintiffs note that the USPTO instructed that the "relevant inquiry is focused on 'whether the sale . . . made the invention available to the public.'" (Id.)

Teva emphasizes that the USPTO guidelines are non-binding on this Court. (See dkt. 226 at 33.) See also Enzo Biochem, Inc., 323 F.3d at 964. Defendant notes that the USPTO acknowledges that the guidelines were issued "as a practical matter" until "the courts . . . ultimately address questions concerning the meaning of AIA 35 U.S.C. § 102." (Id. (quotation and citation omitted).) Defendant argues that because the USPTO

intended these guidelines only to serve as temporary guidance, the Court need not consider them. (See id.)

Plaintiffs reply that it is significant that the USPTO arrived at the same interpretation of § 102(a)(1) as the Plaintiffs "after a comprehensive study, which included a thorough analysis of the legislative history." (See dkt. 236 at 14.) Plaintiffs note that the USPTO's interpretation of the AIA should not be "downplay[ed]." (See id.)

3. Legislative history

Plaintiffs argue that the legislative history confirms their plain meaning interpretation of § 102(a)(1). (See dkt. 209 at 22.) They note that the Committee Report is "the most persuasive [source] . . . on the bill in question" because it incorporates by reference the Senate hearings in which the AIA's sponsor, Senator Kyl, explained the AIA's on-sale bar. (See id. at 22–24.) Plaintiffs claim that Senator Kyl's statements in these hearings highlight the congressional intent to require that a claimed invention be made available to the public in order for the on-sale bar to apply. (See id. at 23.) Plaintiffs cite the record from the March 8, 2011 Senate hearing in pertinent part: "The word 'otherwise' makes clear that the preceding clauses describe things that are of the same quality or nature as the final clause—that is, although different categories of prior art are listed, all of them are limited to that which makes the invention 'available to the public.'" (Dkt. 236-3 at 16 (Mar. 8, 2011 Congressional Record).) In a September 8, 2011 hearing on the final bill, Senator Kyl stated:

> As Chairman Smith most recently explained in his June 22 remarks, "contrary to current precedent, in order to trigger the bar in new 102(a) in our legislation, an action must make the patented subject matter 'available to the public' before the effective filing date." . . . When the committee included the words "or otherwise

> available to the public" in section 102(a), the word "otherwise" made clear that the preceding items are things that are of the same quality or nature. As a result, the preceding events and things are limited to those that make the invention "available to the public."

(Id. at 237 (Sept. 8, 2011 Congressional Record).)

Defendant sets forth two arguments in opposition to the Plaintiffs: (1) the AIA is a culmination of Congress's prior attempts to enact patent reform in 2005, 2007, 2008, and 2009—all of which left the on-sale bar unchanged; and (2) Plaintiffs' interpretation of the AIA's legislative history improperly relies on a "minority view." (See dkt. 226 at 22–31.)

Teva notes that attempts were made in 2005 and 2008 to "expressly change[] the on-sale bar to exclude non-public sales, and did not pass." (Id. at 23.)[45] Other attempts at patent reform, particularly in 2007 and 2009, retained the "public use" and "on sale" categories of prior art. (See generally id. at 23–27.)[46] Defendant argues that the House's 2007 patent reform bill maintained the on-sale bar because of "how the terms 'in public use' and 'on sale' have been interpreted by the courts" and because "there is nothing inherent in a first-to-file system that will deter inventors from making use of their inventions as trade secrets and then some time later filing a patent application for the

[45] The wording of this rejected amendment defined invalidating prior art as that which is "patented, described in a printed publication, or otherwise publically [sic] known." (See dkt. 226 at 23.) The 2008 proposed amendment defined invalidating prior art as that which is "patented, described in a printed publication, or otherwise made available to the public (other than through testing undertaken to reduce the invention to practice)." (See id. at 25 (citation omitted).)

[46] The proposed wording of the 2007 and 2009 amendments defined invalidating prior art as that which is "patented, described in a printed publication, or in public use, on sale, or otherwise available to the public." (See id. at 25–27.)

invention." (See id. at 24 (citation omitted).) Teva notes that despite the inclusion of the phrase "otherwise available to the public" in the 2007 and 2009 bills, Senator Kyl objected to the 2009 Senate bill because the bill should have removed any "patent-forfeiture provisions that apply only to non-public prior art." (See id. at 27.) Defendant argues that this objection thus indicates that Senator Kyl was aware that the phrase "otherwise available to the public" still included secret prior art. (See id.)

Plaintiffs state that the Defendant attempts to minimize the sponsoring Senator's statements but "do[es] not cite a single statement from any congressperson that either rebuts the portions of the legislative history that Plaintiffs cite or affirmatively supports their statutory interpretation." (See dkt. 236 at 10.) Plaintiffs also note that Defendant cannot point to any support for its position in the Committee Report, "[d]espite its importance to statutory interpretation . . . ." (See id. at 12.) Plaintiffs claim that Defendant's arguments regarding prior patent reform bills are "based on mischaracterizations . . . and misleading inferences . . . ." (See id.) Plaintiffs clarify that only the 2007 patent reform bill "purport[ed] to 'maintain' the pre-AIA on-sale bar." (See id. at 13.)

4. Public policy considerations

Plaintiffs argue that the AIA's overhaul of the United States patent system, i.e., converting from a first-to-invent to a first-inventor-to-file system, comports with the policy underlying the changes to the on-sale bar. (See dkt. 209 at 24–25.) Plaintiffs note that under the prior first-to-invent system, "there was a need to prevent an inventor from commercially exploiting the invention substantially beyond the statutory term through first conducting secret

sales or offers for sales, and then filing a patent application." (Id. at 25.) Under the first-to-invent system, the on-sale bar deterred "an inventor's attempt to commercialize his invention beyond the statutory term." (Id. (quotation and citation omitted).) The first-inventor-to-file system, however, adequately incentivizes an inventor to promptly apply for a patent because "the applicant risks having her invention patented by another that may have invented later." (See id. (quotation and citation omitted).)

Defendant critiques Plaintiffs' policy argument, stating that "this narrow view ignores the broader policy principles of the on-sale bar, which continue after the AIA." (See dkt. 226 at 31.) Defendant argues that the on-sale bar still functions as a deterrent for secret commercialization because "there is nothing inherent in a first-to-file system that will deter inventors from making use of their inventions as trade secrets and then some time later filing a patent application for the invention." (See id. at 32.) Defendant notes that Plaintiffs' proposed interpretation of § 102(a)(1), in which commercialization does not "affect[] the inventor's right to seek patent protection later," would have the opposite effect of encouraging secrecy. (See id.)

Plaintiffs maintain that the AIA's amendments reflect a significant shift in Congress's prioritization of certain policies underlying patent law. (See dkt. 236 at 14.) Plaintiffs argue, with respect to the Defendant's arguments that the first-inventor-to-file system has no effect on secret commercialization, that the AIA's prior-use defense allows "secret uses of one's proprietary technology." (See id. at 15.) Plaintiffs claim that the expansion of the prior-use defense enables secret uses without "forcing the first inventor

to file a patent application" or "risk[ing] infringement under the 'first-inventor-to-file' system." (See id.) Thus, Plaintiffs contend, Congress intended the different provisions of the AIA to function together such that the on-sale bar now applies only to "publicly accessible" prior art. (See dkt. 236-3 at 84 (AIA Committee Report) ("[T]he phrase 'available to the public' is added to clarify the broad scope of relevant prior art, as well as to emphasize the fact that it must be publicly accessible.").)

The Court, having considered the parties' arguments on the plain language meaning of § 102(a)(1), the USPTO's guidelines, the undisputed AIA Committee Report, and the public policy considerations underlying the passage of the AIA, concludes that § 102(a)(1) requires a public sale or offer for sale of the claimed invention. The new requirement that the on-sale bar apply to public sales comports with the plain language meaning of the amended section, the USPTO's interpretation of the amendment, the AIA Committee Report, and Congress's overarching goal to modernize and streamline the United States patent system. (See dkt. 236-3 at 83–84 (AIA Committee Report).)

2. Findings as to sale or offer to sell pre-AIA

The Court will now make findings on the "sale or offer to sell" prong as to the '724, '725, and '424 patents, which are subject to the pre-AIA on-sale bar. For purposes of the pre-AIA on-sale bar, the Court finds that the MGI Supply Agreement constitutes a sale because it was a contract for a future commercial product. See U.C.C. § 2-105(2) ("purported present sale of future good or of any interest therein operates as a contract to sell"). The fact that the clearly-described "products" had not yet received FDA approval

at the time of the contracting does not change this conclusion. See Section II.A.3. Moreover, because the sale was made more than one year prior to the application date of the patents-in-suit, the MGI Agreement satisfies the pre-AIA sale prong under Pfaff. See Pfaff, 525 U.S. at 67. The Court will now consider whether Helsinn's agreements with Oread and SP ("Oread and SP Agreements") also satisfy the sale prong of the pre-AIA on-sale bar.

a. Applicable legal standards

The Court notes that during the bench trial in this case, the Federal Circuit issued an opinion in Medicines Co. v. Hospira, Inc., 791 F.3d 1368 (Fed.Cir. 2015), vacated by Medicines Co. v. Hospira, 805 F.3d 1357 (Fed.Cir. 2015), which addressed the issue of whether a sale for services constitutes a commercial sale under the pre-AIA on-sale bar. See id. at 1371. After closing arguments in this case, the Federal Circuit vacated its opinion in Medicines Co. and granted that plaintiff's petition for rehearing en banc. See Medicines Co., 805 F.3d at 1358. The Court notes that the issue of what constitutes a commercial sale under the pre-AIA on-sale bar remains in flux at this time. See id.

The facts underlying the district court's holding in Medicines Co. arose from ANDA litigation in which the ANDA applicant alleged, inter alia, that the patents-in-suit were invalid under the on-sale bar. See Medicines Co., 791 F.3d at 1370.[47] The Medicines Company hired Ben Venue to prepare batches of bivalirudin, a synthetic

[47] A summary of the facts of Medicines Co. is provided in this Memorandum Opinion as the parties relied heavily on this case during their closing arguments. (See generally dkt. 353.) The prior ruling in Medicines Co. will be referenced by the Court only in the context of the parties' arguments.

peptide used as an anticoagulant, "using an embodiment of the patented method." See id. at 1369. The batches were for both commercial and clinical packaging. See id. at 1370. The Medicines Company acknowledged that "each batch had a commercial value of over $10 million." See id. at 1371. The ANDA applicant alleged that the claimed invention was commercially offered for sale before the critical date. See id. at 1370. The district court found, inter alia, that the patents-in-suit were not invalid under the on-sale bar because: (1) the patentholder had only contracted with a manufacturing company for the sale of "manufacturing services"; and (2) the developmental batches manufactured under the agreement fell under the experimental use exception of the on-sale bar. See id. At issue on appeal is whether these facts constitute a commercial sale under the pre-AIA on-sale bar.[48]

The facts set forth in Medicines Co. are distinguishable from Trading Technologies International, Inc. v. eSpeed, Inc., 595 F.3d 1340 (Fed.Cir. 2010). In Trading Technologies, an inventor hired Trading Technologies ("TT") to build trading software in accordance with the inventor's idea. See Trading Techs., 595 F.3d at 1361.

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[48] The Federal Circuit requested briefing on the following issues:

> (a) Do the circumstances presented here constitute a commercial sale under the on-sale bar of 35 U.S.C. § 102(b)?
>
> (i) Was there a sale for the purposes of § 102(b) despite the absence of a transfer of title?
>
> (ii) Was the sale commercial in nature for the purposes of § 102(b) or an experimental use?
>
> (b) Should this court overrule or revise the principle in Special Devices, Inc. v. OEA, Inc., 270 F.3d 1353 (Fed.Cir. 2001), that there is no "supplier exception" to the on-sale bar of 35 U.S.C. § 102(b)?

Medicines Co., 805 F.3d at 1358.

TT built the customized software and the inventor paid TT for this custom software. See id. The patent challenger argued that the inventor's consulting agreement with TT invalidated the patent-in-suit under the on-sale bar. See id. The Federal Circuit held that the parties' consulting agreement was not a sale under the on-sale bar because "TT promised to develop trading software for [the inventor] because he lacked the technical expertise to do so." See id. The court held that "[i]nventors can request another entity's services in developing products embodying the invention without triggering the on-sale bar." Id. The court noted, in so holding, that an inventor's request to manufacture a product for "secret, personal use could not constitute a sale under 35 U.S.C. § 102(b)." See id.

"[A] sale is a contract between parties to give and to pass rights of property for consideration which the buyer pays or promises to pay the seller for the thing bought or sold." Bone Care Int'l, LLC v. Pentech Pharms., Inc., 2012 WL 1068506, at *6 (N.D. Ill. Mar. 29, 2012) (quoting In re Caveney, 761 F.2d 671, 676 (Fed.Cir. 1985)). In Bone Care, the patentholder entered into a supply agreement with a manufacturer to produce batches of vitamin D_2 that the patentholder was "stockpiling for the purposes of commercialization after FDA approval of Bone Care's first NDA." Id. at *6. The court compared these facts to Trading Technologies, emphasizing that the contract "was not for services rendered . . . but explicitly set forth terms related to the sale of goods." Id.

b. Parties' arguments

Helsinn first argues that the Oread and SP Agreements were service contracts, in which Oread and SP provided services like manufacturing, formulation development, and analytical development to Helsinn. (See dkt. 353 at 96.) Helsinn analogizes this case to Trading Technologies, wherein the Federal Circuit held that inventors may request another entity to perform services without violating the on-sale bar. (See id.) See also Trading Techs., 595 F.3d at 1361. Helsinn asserts that its agreements with Oread and SP were similar in that they were for the development of products embodying the '219 patent. (See dkt. 353 at 98.)

Helsinn also argues that the Oread and SP Agreements were for developmental batches of its product, thus falling outside the "commercial sale" scope of the on-sale bar. (See id. at 97.) Helsinn distinguishes Medicines Co., noting that the commercial batches produced in Medicines Co. violated the on-sale bar because "[t]hey were stockpiled," marked with commercial numbers, and ready for shipping in anticipation of a launch. (See id. at 97–98.) Helsinn notes that the Oread and SP Agreements did not contemplate the purchase and sale of commercial batches; rather, the agreements were used "for clinical development, . . . stability testing," and other services "en route to seeking FDA approval." (See id. at 98.) Helsinn emphasizes that a pre-AIA analysis that invalidates patents based upon these developmental supplier agreements carries dangerous public policy implications because:

> Small companies like Helsinn rely extensively on contract manufacturing organizations during the development process of getting a pharmaceutical product to the market . . . . [I]f we are to invalidate patents based on use of CMOs [contract manufacturing organizations], there's going to be an awful lot of pharmaceutical patents that are in trouble out there that were never shown to work for their intended purpose during that developmental phase . . . .

(Id. at 99.)

Teva argues that the Oread and SP Agreements were "clearly binding commercial contracts" because the agreements set forth contractual terms like price and quantity. (See id. at 10–12.) Teva notes that Helsinn's interpretation of the Oread and SP Agreements as service contracts is tantamount to "characteriz[ing] any sale of a product as a service contract." (See id. at 12.) Teva relies upon the Federal Circuit's holding in Medicines Co., although as this Court has noted, the Federal Circuit vacated this opinion after the parties' closing arguments in this case. Teva also notes that Bone Care is instructive in this case as the court held that the supply agreement between the parties "was not for services rendered . . . but explicitly set forth terms related to the sale of goods." Bone Care, 2012 WL 1068506, at *6. (See also dkt. 353 at 30.)

With respect to Helsinn's argument that the on-sale bar does not apply to contracts for development batch manufacturing, Teva asserts that Helsinn has "expressly stipulated that they are not asserting the experimental use doctrine." (See dkt. 353 at 21; see also dkt. 317 at 2.) Teva also notes that the on-sale bar does not provide any "carve out for . . . CMOs or development agreements." (See dkt. 353 at 21.) Teva argues that in similar cases where the company did not have the manufacturing ability to develop its own drug

product, such as Bone Care and Medicines Co., the courts found that these agreements qualified as "sales" under the on-sale bar. (See id. at 30.)

c. Analysis

The only issue that this Court will address in this subsection is whether the Oread and SP Agreements constitute a commercial sale or offer for sale under the pre-AIA on-sale bar. See 35 U.S.C. § 102(b). The Court, taking into consideration the parties' arguments and the unsettled law in this area, finds that the Oread and SP Agreements are not sales or offers for sale under the pre-AIA on-sale bar.[49]

The nexus of the parties' disagreement lies in whether the stockpiling for development processes like clinical trials one year prior to a patent's critical date constitutes a commercial sale or offer for sale under the on-sale bar. Helsinn argues that contracts that supply a company with its developmental batches for clinical trials and data-gathering cannot be considered a commercial sale or offer for sale. (See, e.g., dkt. 353 at 99.) Teva counters that Helsinn seeks to carve out a novel exception to the on-sale bar, and that "paying to have the product made . . . is starting to convert his invention into something that can be commercialized . . . ." (See id. at 21; id. at 30.)[50]

[49] The Court agrees with Teva that Helsinn's argument that the Oread and SP Agreements were merely service contracts invites a slippery slope analysis in which this Court declines to engage. (See dkt. 353 at 12 ("[Y]ou could characterize any sale of a product as a service contract.").)

[50] Although not briefed by the parties, the Federal Circuit's rehearing en banc of Medicines Co., particularly on the issue of whether a supplier exception to the on-sale bar exists, may be instructive in these pharmaceutical patent cases with facts analogous to this case or Medicines Co. This Court cannot, however, read the tea leaves on the outcome of the Medicines Co. rehearing and will not do so here.

The sparse case law on this issue is distinguishable in part from this case, although the Court does bear in mind some similarities.[51] Unlike Trading Technologies, Oread and SP Agreements were not entered into for the purpose of Helsinn conducting its own "secret, personal use" of its product. See Trading Techs., 595 F.3d at 1362. But, similar to Trading Technologies, the Court finds that these agreements were not for the commercialization of Helsinn's product. (See dkt. 322 at 125, 129.) Unlike Bone Care, the Oread and SP Agreements were not entered into for the purpose of stockpiling a commercial product while anticipating FDA approval and a commercial launch. See Bone Care, 2012 WL 1068506, at *3. This case is similar to Bone Care in that both Bone Care and Helsinn lacked their own manufacturing capacity, and Helsinn's acknowledgement that the developmental batches were "commercial" in size is comparable to developmental batch "stockpiling." (See dkt. 312 at 19–20.)

The Court reverts back to the Pfaff test, which requires a claimed invention to be the subject of a "commercial offer for sale." See Pfaff, 525 U.S. at 67. There is no dispute that Helsinn and Oread, and later Helsinn and SP, entered into binding contracts for the manufacture of developmental batches of palonosetron, including "commercial scale" batches to satisfy NDA requirements. But the Court finds nothing in these agreements to suggest the contracts contemplated a commercial sale of any of those batches. (See, e.g., dkt. 322 at 125, 129.) Unlike Bone Care, Helsinn was not stockpiling its commercial product, or anticipating a launch with those batches pending FDA

[51] As noted above, the Court is not considering the Federal Circuit's prior ruling in Medicines Co. for purposes of this analysis.

approval. See Bone Care, 2012 WL 1068506, at *6 (quotation omitted) ("Bone Care was stockpiling for the purposes of commercialization after FDA approval of [its] first NDA."). Rather, Helsinn entered into the Oread and SP Agreements for the purpose of pursuing FDA approval, which includes, as Dr. Calderari testified, "analytical development, formulation development, batches preparation for clinical trials, and stability data generation." (Dkt. 322 at 122.)

The Court also finds compelling Helsinn's argument that many pharmaceutical companies rely upon the outsourcing of developmental batch manufacturing before the commencement of clinical trials. (See dkt. 353 at 99.) While the on-sale bar is intended to prevent the commercial exploitation of a patent prior to its critical date, the Court does not see how supply agreements for developmental batches can reasonably be considered commercial exploitation when, particularly in the pharmaceutical field, the developmental batches are critical to pre-commercialization steps, like clinical trials, formulation development, and manufacturing quality requirements. See, e.g., D.L. Auld Co. v. Chroma Graphics Corp., 714 F.2d 1144, 1147 (Fed.Cir. 1983). (See also dkt. 322 at 122.) In this case, the Court finds a marked difference between the commercial stockpiling in Bone Care and the developmental batches that were manufactured in this case.

The Court finds, for the above-stated reasons, that the Oread and SP Agreements do not constitute sales under the pre-AIA on-sale bar.

3. Findings as to sale or offer to sell post-AIA

As this Court has interpreted the post-AIA on-sale bar, the "sale" prong of the on-sale bar is satisfied by a public sale or offer for sale of the claimed invention. See, e.g., 35 U.S.C. § 102(a)(1) (barring patentability if "the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public").

The Court has found in Section II.A.2 that the Oread and SP Agreements were not "sales" under the pre-AIA on-sale bar. The Court further finds that the Oread and SP Agreements were not "public" sales under the post-AIA standard, because they were entirely subject to and performed under confidentiality restrictions. See Sections I.C.4 and I.C.8.

The Court will next consider whether the MGI License Agreement and the MGI Supply Agreement (collectively, "MGI Agreement") satisfies the post-AIA on-sale bar sale prong.

a. Legal standard

An agreement that "relates specifically to [a] supply of . . . worldwide requirements for what are clearly commercial purposes . . . constitutes an offer to sell that has been accepted." Enzo Biochem, Inc. v. Gen-Probe, Inc., 424 F.3d 1276, 1282 (Fed.Cir. 2005) ("Supply of worldwide requirements at reasonable times and prices surely means commercial supply . . . ."). In Enzo, the patentholder entered into an agreement that provided, "Enzo shall supply to Ortho and Ortho shall purchase from Enzo for use in

Licensed Products no less than ninety percent (90%) of Ortho's United States requirements or seventy-five percent (75%) of Ortho's worldwide requirements of Active Ingredients . . . ." Id. at 1279.

Enzo argued that the agreement was vague and did not require Ortho to purchase the patent's embodiment exclusively from Enzo. See id. at 1282. The patent challenger alleged that the agreement "created the necessary contractual obligations on the parties to constitute a commercial offer for sale." Id. at 1281. The Federal Circuit held that:

> Enzo's claimed invention, the polynucleotide probe, is a tangible item or product that can be sold or offered for sale. The language of that provision clearly imposes upon Enzo the obligation to sell and on Ortho the obligation to purchase a significant percentage of its U.S. and worldwide requirements of the product labeled "Active Ingredients." There is no doubt that paragraph 2.14 constitutes a binding commitment by the parties to enter into a commercial sale and purchase relationship.

Id.

The Federal Circuit also emphasized that Enzo's emphasis of the context of this particular sale provision was inapposite and "d[id] little to alter the plain language of that provision in the agreement." See id. at 1282.

The determinative factor under the sale prong of the on-sale bar is the contractual language of the agreement. See generally Apotex, Inc. v. Cephalon, Inc., 2011 WL 6090696 (E.D. Pa. 2011). In Apotex, the patentholder entered into a supply and license agreement in which its supplier had the "right to sell modafinil, a pharmaceutically active compound . . . and Cephalon wishes to purchase the Compound from Lafon." Id. at *15. The court found that the agreement's language was analogous to the Enzo agreement in

that both provided for a "free supply of product for clinical testing," and "contain[ed] language akin to a requirements contract," including "to purchase" and "to sell." Id. at *16. The court also noted that any mention of research and development in the contract was "incidental to the primary commercial purpose of the contract . . . ." See id.

Conversely, an agreement may not be considered a sale or offer for sale under the on-sale bar if the agreement lacks material terms that are common to commercial documents. See Elan Corp. v. Andrx Pharms., Inc., 366 F.3d 1336 (Fed.Cir. 2004). In Elan, the patentholder sent letters to various entities stating that Elan was seeking a partner in planning clinical studies. See id. at 1337–38. The letter also discussed granting a license and a pricing structure without any specific price term. Id. at 1341–42. The product at issue in Elan, a formulation of naproxen for the treatment of inflammation and pain, had not yet been patented or received FDA approval at the time of the letters being sent. See id. at 1337. The Federal Circuit concluded that there was no offer for sale in the letters because "an offer to enter into a license under a patent for future sale of the invention covered by the patent when and if it has been developed . . . is not an offer to sell the patented invention that constitutes an on-sale bar." Id. at 1341. The court noted that the letter did not contain "any mention of quantities, time of delivery, place of delivery, or product specifications beyond the general statement that the potential product would be a 500 mg once-daily tablet containing naproxen." Id.

b. Parties' arguments

Helsinn first argues that the on-sale bar does not apply because the MGI Agreement was indefinite as to the product that was going to be manufactured. (See dkt. 353 at 100–01.) The MGI Agreement defined "Products" as "the pharmaceutical preparations for human use in I.V. dosage form containing the Compound as an active ingredient in the formulation that will be described in the Registration . . . ." (DTX-115-0007.) Helsinn analogizes this case to Elan, arguing that in both cases, the product was unspecified at the time the agreement was formed, and it was unclear as to whether a product actually existed at the time of the alleged offer for sale. (See dkt. 353 at 102.) Helsinn would distinguish Enzo from this case, arguing that "[t]he product at issue in [the Enzo] agreement was real. It was tangible. It was set in concrete." (See id.)

Helsinn next argues that the MGI Agreement never made the claimed invention available to the public prior to the critical date, thus never triggering the on-sale bar. (See dkt. 209 at 29; dkt. 353 at 87–88.) Helsinn argues as a threshold matter that the on-sale bar requires disclosure of the claimed invention, rather than the fact that a sale has merely occurred or will occur. (See dkt. 353 at 88.) Helsinn asserts that in order for a claimed invention to become available to the public and trigger the on-sale bar, the "very specific set of claim limitations" must be disclosed. (See id.)

Here, Helsinn notes that the MGI Agreement was executed in private and contained confidentiality provisions. (See dkt. 209 at 30.) Helsinn argues that its press releases and MGI's Form 8-K filed with the Securities and Exchange Commission were

redacted and only contained information that "two parties [we]re working on the palonosetron product." (See dkt. 353 at 88.) Helsinn also emphasizes that the press releases and the Form 8-K failed to "disclose[] any aspect of the claimed invention of the '219 patent other than the use of the active ingredient palonosetron, which was already known in the prior art." (See dkt. 209 at 30.) Helsinn concludes that because the claimed invention itself, i.e., Helsinn's palonosetron formulation, was never made available to the public, the on-sale bar has not been satisfied as it relates to the MGI Agreement. (See id.)

Teva argues that the MGI Agreement constitutes a sale or offer for sale under the on-sale bar. (See dkt. 353 at 18–19.) Teva first argues that the language of the agreement, on its face, requires a finding that the agreement is a requirements contract "that easily satisfies the Pfaff requirement of a 'commercial offer for sale.'" (See dkt. 226 at 35; see also dkt. 353 at 18.) In support of its contention, Teva notes that the MGI Agreement includes contract terms for product, quantity, and price for the "sale of Helsinn's palonosetron product that is an embodiment of the asserted claims of the '219 patent." (See dkt. 226 at 35.)

Teva also asserts that this case is analogous to Enzo insofar as Helsinn argues that the uncertain product defined in the MGI Agreement negates applicability of the on-sale bar. (See dkt. 353 at 19.) Teva notes that the Federal Circuit, in Enzo, summarily dismissed the patentholder's vagueness argument because the contract imposed "upon Enzo the obligation to sell and on Ortho the obligation to purchase . . . ." See Enzo, 424 F.3d at 1282. Teva argues that the language of the MGI Agreement, regardless of the

definition of Helsinn's palonosetron product, set forth contractual terms under which both parties were bound. (See dkt. 353 at 18.)

With respect to Helsinn's threshold argument, i.e., that every claim limitation of the claimed invention must be made available to the public for a sale or offer for sale to satisfy the on-sale bar, Teva states that this "is not the law now, and has never been." (See id. (citation omitted).) Teva argues that even under the post-AIA on-sale bar, the MGI Agreement invalidates the '219 patent because: (1) MGI was a member of the public at the time of the agreement; and (2) MGI's Form 8-K "discloses Helsinn's binding commercial sales agreement with MGI for the palonosetron product." (See dkt. 226 at 39–40.)

Teva first argues that "[t]he Federal Circuit has repeatedly held that for purposes of the on-sale bar, the 'public' is broadly defined and includes an independent party, not controlled by the seller, entering into an arms-length sales agreement for the later-patented good." (Id. (citations omitted).) Teva argues that because MGI is an independent entity and entered into an agreement with Helsinn, the sale was therefore available to the public. (See id. at 39.) Moreover, Teva asserts that MGI's Form 8-K "makes clear" that Helsinn had contracted to supply MGI's requirements for the palonosetron product for a price, so that MGI could in turn resell that product. (See id. at 40.) Teva notes that the "Product" disclosed in the MGI Agreement "embodies each of the asserted claims of the '219 patent," which satisfies the sale prong of the on-sale bar. (See id.)

c. Analysis

The Court is not persuaded by Helsinn's argument that the on-sale bar does not apply because the product defined in the MGI Agreement was indefinite or uncertain because it had not yet received FDA approval. (See dkt. 353 at 100–02.) The Court is guided by Enzo and Apotex, in which the Federal Circuit held that the sale prong of the on-sale bar is satisfied if an agreement between parties is for a commercial purpose (i.e., a sale or offer for sale) and contains contractual language. See Enzo, 424 F.3d at 1282; Apotex, 2011 WL 6090696, at *16.

Here, Helsinn and MGI entered into a Supply and Purchase Agreement for the sale of Helsinn's commercial palonosetron product. (See dkt. 226 at 14.) The MGI Supply Agreement contained contractual terms relating to Helsinn's product, the quantity of product that would be sold to MGI, and at which price. (See id. at 35.) It is inapposite that at the time of the agreement, the product was uncertain and awaiting FDA approval, because the appendices to both the MGI License Agreement and the MGI Supply Agreement specified the exact dosages and concentrations that were in the pending FDA filings. See Section I.C.9. (See dkt. 353 at 100–02.) Indeed, under a pre-AIA analysis, the Court's analysis would end here with a conclusion that the MGI Agreement constituted a contract for sale, thus satisfying the "sale" prong of the on-sale bar.

However, the post-AIA on-sale bar also requires that the sale or offer for sale make the claimed invention available to the public. See 35 U.S.C. 102(a)(1) (barring patentability if "the claimed invention was patented, described in a printed publication, or

in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention"). It is not sufficient that a sale or offer for sale merely occur.[52]

The Court finds that the MGI Agreement did not make the claimed invention available to the public. Teva asserts that the Form 8-K and Helsinn's press releases made the existence of the agreement available to the public. (See dkt. 226 at 40–41.) However, MGI's Form 8-K was redacted and indicated only that Helsinn and MGI had entered into an agreement to purchase Helsinn's product. (See, e.g., dkt. 226 at 14.) Additionally, Helsinn's press releases only disclosed the existence of the agreement between Helsinn and MGI. (See id.) Insofar as these documents publicized the parties' MGI Agreement, Teva is correct. But the post-AIA on-sale bar inquiry is not focused on the public disclosure of the sale or offer for sale; rather, the "sale" prong of the on-sale bar requires that the sale make the claimed invention available to the public one year prior to its critical date. Teva has failed to show how MGI's Form 8-K or Helsinn's press releases on the MGI Agreement made Helsinn's claimed invention, i.e., its palonosetron formulation, available to the public. See Section I.A.9.

The Court finds, for the reasons stated above, that the post-AIA on-sale bar does not apply to the MGI Agreement because the sale or offer or sale did not make Helsinn's claimed invention available to the public one year prior to the critical date.

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[52] This Court is further bolstered by the USPTO's interpretation of the post-AIA on-sale bar, in which the USPTO concluded, "the sale must make the invention available to the public." See Examination Guidelines for Implementing the First Inventor to File Provisions of the Leahy-Smith America Invents Act, 78 Fed. Reg. 11,059, 11,075 (Feb. 14, 2013) (to be codified at 37 C.F.R. 1).

4. Findings on ready for patenting

The Court, having considered the "sale" prong of the on-sale bar under both pre-AIA and post-AIA standards, will now consider whether the patents-in-suit were ready for patenting by the critical date of January 30, 2002. See Pfaff, 525 U.S. at 67–68. The parties agree that the "ready for patenting" prong under Pfaff has remained unchanged by the AIA. (See dkt. 353 at 37, 119.)

a. Legal standards

In Pfaff, the Supreme Court held that an invention may be ready for patenting in two ways: (1) "proof of reduction to practice before the critical date;" or (2) "by proof that prior to the critical date the inventor had prepared drawings or other descriptions of the invention that were sufficiently specific to enable a person skilled in the art to practice the invention." See Pfaff, 525 U.S. at 67–68. To demonstrate reduction to practice, a party must prove that the inventor (1) "constructed an embodiment or performed a process that met all the limitations" and (2) "determined that the invention would work for its intended purpose." Z4 Techs., Inc. v. Microsoft Corp., 507 F.3d 1340, 1352 (Fed.Cir. 2007).[53] As patents are presumed valid, the patent challenger must prove by clear and convincing evidence that the claimed formulation was ready for patenting at the time of the critical date. See SRAM Corp. v. AD-II Eng'g, Inc., 465 F.3d 1351, 1357 (Fed.Cir. 2006).

[53] The Court will focus on whether the claimed invention was reduced to practice, i.e., shown to work for its intended purpose, as this was the central issue disputed by the parties. (See, e.g., dkt. 353 at 37; id. at 102.)

Whether a claimed formulation has been reduced to practice is a fact-driven analysis that may require an analysis of the parties' claim construction. See, e.g., Mitsubishi Chem. v. Barr Labs., Inc., 435 Fed.Appx. 927, 934–35 (Fed.Cir. 2011); Allergan, Inc. v. Sandoz, Inc., 2011 WL 1599049 (E.D. Tex. Apr. 27, 2011). In Mitsubishi, the district court interpreted the claim "pharmaceutical composition for injection" to mean "a composition that is suitable for treating medical conditions by injection." Mitsubishi, 435 Fed.Appx. at 934 (quotation omitted). The patent challenger argued on appeal that the claim should have been interpreted as "a medicinal drug composition that can be administered by injection." See id. The patent challenger cited precedent in which the Federal Circuit had construed the term "pharmaceutical" to mean "medicinal drug." See id. (citing to Novartis Pharms. Corp. v. Eon Labs Mfg., Inc., 363 F.3d 1306 (Fed.Cir. 2004)). The court distinguished Mitsubishi from Novartis, noting that the claim limitation at issue in Novartis was a preparation claim and thus did not apply to the composition claim at issue in Mitsubishi. See id. The court further noted that "[c]laims to pharmaceutical compositions are typically distinct from claims to medicinal compounds themselves." See id. (internal quotation omitted). The Federal Circuit affirmed the district court, noting that "[t]he specification does not require this restrictive construction, nor is this property necessary for patentability." Id.

In Allergan, the parties disputed whether the claim construction at issue should include the additional limitation of "with a drug that meets FDA standards for approval." See Allergan, 2011 WL 1599049, at *8. The patent challenger argued that "in the United

States, a patient cannot be legally treated with a drug that is not approved by the FDA." Id. The district court found that "it would be improper to read this limitation into the claims," because "FDA approval is irrelevant to proceedings before the [PTO]." See id.; see also AstraZeneca v. Apotex, 633 F.3d 1042, 1061 (Fed.Cir. 2010) (noting that, in an induced infringement case, the FDA's opinion regarding a proposed label amendment was inapposite because "the FDA is not the arbiter of patent infringement issues").

In other cases, a factual determination as to whether a formulation was ready for patenting, i.e., reduced to practice, may hinge on the timeline and completion of the formulation's clinical studies. See, e.g., In re Omeprazole Patent Litig., 536 F.3d 1361, 1372 (Fed.Cir. 2008) ("The district court found that the claimed formulation was not reduced to practice before the clinical trials were completed, and we uphold that finding."); Estee Lauder Inc. v. L'Oreal, S.A., 129 F.3d 588, 594–95 (Fed.Cir. 1997) ("[W]hen testing is necessary to establish utility, there must be recognition and appreciation that the tests were successful for reduction to practice to occur."); Bayer Schering Pharma AG v. Barr Labs., Inc., 2008 WL 628592, at *44 (D.N.J. Mar. 3, 2008) ("The extensive clinical testing demonstrates that there was a lack of confidence that the efficacy of the claimed invention could be based solely on the European trials."), aff'd on other grounds, 575 F.3d 1341, 1346 (Fed.Cir. 2009) (stating the "adverse rulings" — concerning the ready-for-patenting prong of the on-sale bar — were not cross-appealed).

In Omeprazole, the claimed formulation that was the subject of the underlying ANDA litigation was created in 1979. See Omeprazole, 536 F.3d at 1372. At that time,

the inventors tested various formulations in order to "create a dosage suitable for commercialization," which included Phase II and Phase III trials. See id. at 1372–73. The patent challenger asserted that the patentholder's clinical trials violated the on-sale bar because "it was known in 1979—the year Astra filed its first patent application for omeprazole—that omeprazole could provide a safe and effective treatment." See id. at 1375.

The district court found that the patentholder's Phase III formulation was not reduced to practice because the inventors had stated that the formulation only "might solve" problems associated with the formulation in earlier clinical trials. See id. at 1373. The district court noted that at the conclusion of Phase III trials, the formulation "still required extensive clinical testing and real-time stability testing to determine whether it could treat gastric acid diseases safely and effectively." Id. at 1373–74. The Federal Circuit affirmed the district court, noting that "[t]he existence of the formulation . . . does not establish that . . . the invention would work for its intended purpose." See id. at 1374–75.

Even if a formulation's clinical trials are fully completed and analyzed, the formulation may not be considered ready for patenting if the completed clinical trials studied a different patient population. See Bayer, 2008 WL 628592, at *43. In Bayer, the patent challenger asserted that the patentholder's claimed invention was invalid because it was in public use, i.e., reduced to practice, during European clinical trials, prior to the patent's critical date. See id. at *13. Unlike the case before this Court, the patentholder

maintained that the United States ("U.S.") clinical trial was an experimental use. Id. at *38. Bayer asserted that its U.S. clinical trials were experimental because: (1) it was unknown whether the formula would be effective in the U.S. population; (2) the U.S. subjects were "far more diverse" than the subjects in the European trials; and (3) it was unknown how the test results between U.S. and European trials would differ. See id.

The court noted in its analysis that the European trials found that "both medications were shown to be effective oral contraceptives." Id. at *42. However, Bayer's experts testified that "the U.S. clinical trials were necessary to determine whether the formula would be effective as an ovulation inhibitor in the U.S. population," citing the populations' differences in "weight, smoking/alcohol habits, and ethnic backgrounds." See id. at *43. The court noted that in Omeprazole, there was insufficient evidence of a reduction to practice because at least one clinical trial had not yet been analyzed. See id. The court held that in the present case, the patent challenger had not shown by clear and convincing evidence that the U.S. clinical trials were not necessary to show the formulation's safety and efficacy. See id. at *44. Accordingly, the court found that "[t]he extensive clinical testing demonstrates that there was a lack of confidence that the efficacy of the claimed invention could be based solely on the European trials." Id.

b. Applied legal standards

The Court will first address the parties' legal analyses of the ready for patenting prong of the on-sale bar. The Court will then address the parties' factual arguments as to whether Helsinn's claimed formulation was ready for patenting before the critical date.

1. Parties' arguments

Helsinn argues that its claimed formulation's treatment-like limitation—"to reduce the likelihood of [CINV]"—renders the Omeprazole holding even more applicable to the case before this Court. (See dkt. 353 at 116–17.) Helsinn notes that the limitation at issue in Omeprazole was a "pure formulation claim," which is a "less compelling" case for a court to require completed Phase III clinical testing. (See id.) Unlike Omeprazole, where the parties had full results from one Phase III study, Helsinn notes that it only had preliminary, unanalyzed Phase III clinical trial results as of January 30, 2002. (See id. at 117.) Helsinn asserts that its treatment limitation makes this a unique case that goes beyond the facts asserted in Omeprazole, and requires fully completed and analyzed Phase III clinical trials to determine whether the invention was effective and ready for patenting. (See id.)

Teva argues that "courts regularly distinguish between patentability and FDA approval." (See id. at 54–55.) In terms of claim construction, Teva highlights Mitsubishi, noting that in that case, the Federal Circuit refrained from equating the term "pharmaceutical" with the FDA classification "safe, effective, and reliable for use in humans." (See id. at 54.) Teva argues that the court so held because FDA approval is irrelevant to a patentability analysis. (See id. at 54–55.)

Teva also argues that Omeprazole is irrelevant because the issue in that case was whether the Phase III formulation was stable. (See id.) Teva notes that Helsinn has stipulated to its claimed formulation's stability, and the only issue on this prong of the on-

sale bar is the formulation's efficacy. (See dkt. 317 at 2.) Teva argues that Omeprazole does not address how fully analyzed and completed Phase III clinical trials are instructive to an efficacy analysis. (See dkt. 353 at 55.) Moreover, Teva notes that nowhere in Omeprazole does the Federal Circuit state that "FDA standards must be met before an invention is ready for patenting." (See id. at 56.)

2. Expert opinions

Dr. Fruehauf

Teva presented opinion testimony of Dr. John Fruehauf on the "ready to patent" prong of the on-sale bar issue. Dr. Fruehauf is an M.D. clinical oncologist with a Ph.D. in pharmacology who teaches, conducts clinical trials, and practices oncology at University of California Irvine and its comprehensive cancer center. He was accepted to testify as an expert in the clinical sciences and pharmacology, with a focus on oncology and supportive care. (Dkt. 324 at 4–14.)[54]

Dr. Fruehauf testified that in his opinion, a person of ordinary skill in the clinical sciences would know as of January 30, 2002 that palonosetron administered to a human reduces the likelihood of CINV. (Id. at 30–31.) The key documents that he discussed in support of that opinion he listed as follows:

- the Phase II 2330 study records;
- the July, 1998 Helsinn Clinical Meeting Minutes;
- the November, 1999 proposed Phase III protocols Helsinn sent to the FDA;
- the September, 2000 Helsinn press release announcing the Phase III start;

[54] Each of the experts who appeared in this trial was eminently qualified to provide the testimony they offered. The Court was highly impressed with each of their credentials and explanations of their opinions, and it was an honor and a pleasure to have them at the trial.

- the Phase III study documents; and
- a declaration later filed with the USPTO [not in the same patent family history] addressing invention timing issues ("Cantoreggi declaration").

(Id. at 33–34.)

Addressing the Phase II study 2330 records, Dr. Fruehauf referred to the text and a table in the Final Report of that study dated July 1995, DTX-0227-0005. He said the design of the study was "a very strong design for a Phase II trial." (Dkt. 324 at 36.) He summarized that the basic objective of the study, as stated in the text, was to determine whether palonosetron, over a dose range of 1 to 90 micrograms per kilogram, given to patients receiving highly emetogenic chemotherapy, would reduce the likelihood of CINV. The primary endpoint to be studied was complete control at 24 hours, defined as no nausea and no vomiting. A secondary endpoint studied was called "complete response," meaning no vomiting but some nausea reported. He pointed to the stated conclusion:

> Palonosetron, administered as a single IV injection of 3, 10, 30 or 90 µg/kg ... was effective in suppressing [CINV] for 24 hours. All four doses were approximately equally effective as compared with the combined results from a cohort of 0.3 and 1 µg/kg.

(Id. at 37.)

Dr. Fruehauf discussed the Complete Control figures in the table presented with that study 2330 conclusion, which is shown here in the margin.[55] He stated that in his opinion, if a person of skill in clinical sciences were to see this Syntex data as of 1995, "it would be clear that the drug at the .25 mg dose [equivalent to 3 mcg/kg in the table] reduced the likelihood of nausea and vomiting." (Id. at 42–44 (bracketed text added).)

He was questioned by counsel for Helsinn about that table, and acknowledged that the "Complete Control" line — the primary endpoint of the study — showed there was no statistically significant difference between results for the bottom doses of 0.3–1 mg and any of the higher doses, including the 3 mcg/kg [0.25 mg] dose, except the 30 mcg/kg [2.1 mg] dose indicated with an asterisk. He said, "[t]hat is correct from a statistical perspective." (Id. at 130–34.) He also confirmed his awareness that in general, the FDA will not allow an indication to be claimed for a drug without a showing of statistical significance of an outcome for the primary efficacy endpoint of a study. (Id.)

[55]

Parameters	RS-25259 Dose (µg/kg)				
	0.3–1	3	10	30	90
% Complete Control (24 hours)	24	46	40	50*	46
% Complete Response (24 hours)	24	39	40	48	46
Median Time (hours) to Failure (first emetic episode or rescue R_x)	5.6	22.7*	19.0	> 24*	21.8*

*statistically significant differences ($p < 0.05$) vs. lowest dose group

(DTX-0227-0015.)

He was also asked if he knew that the Syntex Formulation Book, as a result of all the analyses of the Phase II studies in May of 1995, recommended a palonosetron dose of 1 milligram for Phase III CINV trials. He said he was not aware of that fact. (Id. at 145–46, citing DTX-0254 and DTX-1023.)

Dr. Fruehauf was also shown the FDA's comments and instructions in the March 10, 1999 meeting with Helsinn, where the FDA said "[d]ue to a lack of dose response in this study, these data are inadequate to serve as pivotal efficacy support," and the FDA allowed Helsinn to re-analyze the 2330 data using historical controls in order to offer it as "supportive data" for efficacy. (Id. at 137–38.) He said in his opinion the FDA made a mistake about that; he said, "I think it [the 2330 study] did have a dose response. I think it was just a misunderstanding on the part of the [FDA] reviewer...." (Id. at 137–38, 198–99 (bracketed text added).)[56] He explained that in his view, because the lowest doses showed low effect (albeit not in statistically significant numbers), and because the next four doses were all equivalent, that was a dose response. (Id. at 198–99.)

The next document Dr. Fruehauf discussed in support of his opinion was the July 1998 Helsinn Clinical Meeting Minutes, reflecting the week-long meeting in Palo Alto,

[56] Here the Court notes that a close review of the 1995 Final Report of the 2330 study shows that the subsequent re-analysis resulted in an Errata statement added to that Report after the re-analysis of the data was conducted and reported in the PALO-00-01 Final Report. The Errata statement, dated August 12, 2002, reported that the table shown in the 1995 Final Report of the 2330 study, see n.55 supra, was actually erroneous because the lines for Complete Control (the primary endpoint) and Complete Response (the secondary endpoint) were reversed. (DTX-0227-0012, -0013.) Thus, looking at the second line of data in the table, which is the actual data for Complete Control according to the Errata, there is not even one statistically significant figure, as shown by the lack of any asterisk in that second line of figures. Of course, Helsinn and the FDA did not know this fact on March 10, 1999 at the "End of Phase II" meeting, or when Helsinn submitted its proposed Phase III protocols dated November 15, 1999.

CA attended by scientists from Helsinn, the former Syntex, and consultants including Dr. Gandara. See n.17 supra and accompanying text. There, the outcome of the meeting was to further study doses of 0.25, 0.75 and 2.0 mg, and corresponding concentrations in a 5 ml solution, for possible use in the Phase III trials. (DTX-0015-0008, -0009.)

Dr. Fruehauf interpreted those discussions to indicate that Helsinn at the time regarded the 0.25 dose as the minimum effective dose, "and they were going to take that with a couple of other doses that were higher into the Phase III study." He also said he agreed with Dr. Gandara's recommendation that "3µg/kg was most likely the correct dose for CINV." (Dkt. 324 at 48–49, citing DTX-0015-0008, -0012.) His basis for that opinion was "[b]ecause I think it's clear from the [Phase II] trial that the .25 milligram dose was the inflexion point, and after that you've saturated the receptors and that that's the minimally effective dose, and you want to avoid higher doses because, as you go up on doses, you're more likely to get side effects." (Id. at 50 (bracketed text added).)

On cross-examination, Dr. Fruehauf agreed that the stated outcome of the 1998 Helsinn Clinical Meeting was to keep the 2.0 mg dose in the selected group, and that dose was equivalent to the 30 mcg/kg dose that was shown as the only statistically significant dose in the Phase II 2330 study primary endpoint data. (Id. at 154–55.) He also acknowledged that although he routinely participates in clinical trials in his medical work, he has never been personally involved in the selection of a specific dosage of a drug in a treatment that was eventually approved by the FDA. (Id. at 111–12.)

Dr. Fruehauf also relied upon his reading of the proposed Phase III protocols that Helsinn submitted to the FDA dated November 15, 1999. (DTX-0293.) He referred to the statement that "[d]ata from [the 2330] study clearly demonstrate that the 3 µg/kg dose of palonosetron is the minimal effective dose in preventing CINV." (DTX-0293-0035 (bracketed text added).) He stated that he agreed with this statement, which was based on the same data shown in the table in the 1995 Final Report (see n.55 supra). He said that in his opinion, if a person of skill were to see this statement to the FDA, "[t]hey would interpret this statement as to indicate that the Phase II study showed that the .25 milligram dose could reduce the risk of nausea and vomiting." (Dkt. 324 at 55–56.) The version of that 2330 study table contained in the November 1999 Phase III protocols, however, carried forward the same lack of statistical significance for Complete Response for any dose except the 30 mcg/kg, equivalent to 2.0 mg, dose. (See DTX-0293-0034.)

Dr. Fruehauf also cited the Helsinn press release of September 14, 2000, announcing the commencement of the Phase III trials. There, the company said, "[t]he Phase II trials demonstrated the efficacy of Palonosetron in the prevention of emesis with no significant side effects...." (Dkt. 324 at 56–57.) He said that in his view, a person of skill in the art would understand from this statement that Helsinn knew that palonosetron reduced the likelihood of emesis. (Id.)

He also recognized, however, that when the database from the earliest of those trials was unblinded but not fully analyzed at the other end of the Phase III trials in January 2002, the Helsinn press release on January 16, 2002 said "[w]e are pleased to

have completed all patient treatment and to have begun analysis of the data collected in the palonosetron clinical program." That press release said "The Phase 2 clinical trial results were promising, and we are hopeful that the Phase 3 Palonosetron data will demonstrate that it can make a difference for cancer patients suffering from CINV." (Id. at 182–83, citing DTX-0040.)

Dr. Fruehauf next discussed the fact that the "preliminary" data tables for PALO-99-03, dated January 7, 2002, which Helsinn sent to the FDA with its letter of February 7, 2002, turned out to be identical to the corresponding final data tables contained in the Clinical Study Report for that trial dated July 19, 2002. Teva's counsel asked him if it would be surprising that those results in the final report were identical to the preliminary analysis. He replied, "[t]hey have to be because this was the pre-stipulated result of the unblinded data which had been locked so it can't change." (Id. at 65.)

He said that fact supported his opinion "[t]hat we have a clear understanding from a Phase II study that .25 was the minimal effective dose that was carried forward into Phase III, and in the Phase III trial, that .25 milligram dose was very effective at reducing the likelihood of CINV in a prospective randomized trial.... Prospective is you plan it in advance, and you do what you plan to do, and you can't change what you plan to do." (Id.) He did not deny, however, that as of January 7, 2002, the figures Helsinn had in hand were preliminary figures only. (Id. at 66.)

The last document relied upon by Dr. Fruehauf for his opinions was a declaration filed by Helsinn in the USPTO on Sept. 2, 2010, in support of a patent application that

was not part of the same patent family history as the patents-in-suit, but it did relate to a proposed method of treatment claim for acute and delayed CINV using a 0.25 mg dose of palonosetron. The first declarant listed was Helsinn executive Sergio Cantoreggi, and the other two declarants were company owners Enrico and Riccardo Braglia. (DTX-0287-0413 ("Cantoreggi declaration").) It stated that Alberto Macciocchi, who was the project manager for the PALO-99-03 study, was then deceased, and the purpose of the declaration was "to establish that Alberto Macciocchi, Enrico Braglia and Riccardo Braglia had conceived the idea to use palonosetron for the treatment of acute and delayed-onset CINV, and had conducted clinical trials in humans to test this idea, at least as early as October 2, 2001." (Id.)

Referring to the Clinical Study Report for PALO-99-03 dated July 19, 2002, attached to the declaration as Exhibit A, the Cantoreggi declaration stated, inter alia:

> 2) We submit this declaration to establish that Alberto Macciocchi, Enrico Braglia, and Riccardo Braglia had conceived the invention defined by claim 1 of this application, and reduced it to practice, before November 16, 2001, the date that Dr. Piraccini published abstract no. 5169 in Blood, vol. 98, no. 11 part 2.
>
> 3) In particular, we submit this declaration to establish that Alberto Macciocchi, Enrico Braglia, and Riccardo Braglia had conceived the idea to use palonosetron for the treatment of acute and delayed-onset CINV, and had conducted clinical trials in humans to test this idea, at least as early as October 2, 2001.
>
> . . . .
>
> 17) Thus, we had conceived the idea to use 0.25 mg. palonosetron for the treatment of acute and delayed-onset CINV, as described in claim 1, at least as early as August 1, 2001 (the date that the study began).

18) Most important, we had successfully tested the method in human patients, and we had done so before October 2, 2001 (the date the study was completed).

19) As reported on page 8 of Exhibit A,

> "Pairwise testing revealed differences between palonosetron 0.25 mg and ondansetron in favor of palonosetron 0.25 mg. for ... number of emetic episodes on Study Days 1, 2, 3 and the time period 0 to 120 hours ..."

(DTX-0287-0413, -0415.)

Dr. Fruehauf testified that his reading of this declaration indicates that Helsinn was saying that "they knew the result, they knew that .25 milligrams was effective to reduce the risk of chemotherapy-induced nausea and vomiting, by October 2nd, 2001." (Dkt. 324 at 71.) The reference to October 2, 2001 is, of course, the "last patient out" date, as stated on the first page of the Clinical Study Report for PALO-99-03 dated July 19, 2002, which was attached to the declaration as Exhibit A. (See DTX-0287-0418.) Dr. Fruehauf opined that in his experience, saying that they had "successfully tested the method in humans ... before October 2, 2001," would mean "that they had some understanding from the result of the study and that it was successful." (Dkt. 324 at 72.)

He gave his theory about how Helsinn could have asked the CRO conducting the clinical trial to do some calculations of broad averages in the blinded data before that "last patient out" date, stating that a person of ordinary skill could do the same calculations if they had access to the data. (Id.) On cross-examination, he said he himself did not know what "reduced to practice" meant in the declaration because it is a legal

term, so he would not know how those declarants interpreted that term. (Id. at 157–58.) He also said that his theory about Helsinn possibly having obtained broad efficacy information about the blinded data prior to the "last patient out" date of October 2, 2001 was not supported by any evidence and was just his speculation. (Id. at 164–65.)

Dr. Fruehauf further testified that the inactive excipients in the Phase III formula would not impact the efficacy of the 0.25 mg dose when administered to a patient. Therefore, he said, if a person of ordinary skill in the clinical sciences understood that the Phase II formulation with 0.25 mg was effective for CINV, he or she would expect the Phase III formulation to behave in a similar fashion. (Id. at 84.)

The ultimate opinion expressed by Dr. Fruehauf was stated as follows:

> I think it would be clear to a person of skill in the clinical arts, based on the Syntex Phase II study, [and] based on unblinded data analysis of PALO-99-03 where that output was January 7th, and Cantoreggi's declaration that would potentially rely on blinded data, that it was clear that the .25 milligram dose reduced the likelihood of chemotherapy-induced nausea and vomiting.

(Id. at 89 (bracketed text added).)

Dr. Fruehauf also stated that he disagreed with the opinions stated by Helsinn's expert, Dr. Peck, to the effect that one would need two prospective randomized blinded trials, fully analyzed, to know that the 0.25 mg dose reduced the risk of CINV as claimed in the '219 patent. He said he considered FDA criteria and Patent Office criteria to be different. He again stated that in his opinion, on the strength of the Phase II study as

confirmed in the first Phase III study, it was clear that the 0.25 mg dose was effective for that purpose. (Id. at 93.)

Dr. Peck

Helsinn presented opinion testimony of Dr. Carl Peck on the "ready to patent" prong of the on-sale bar issue. Dr. Peck is an M.D. with board certifications in internal medicine and in clinical pharmacology who also had a Fulbright fellowship in physical chemistry and a research fellowship in clinical pharmacology focused on pharmacokinetics and biostatistics and involving clinical trials. For many years he was in the U.S. Army, practicing medicine and researching and teaching. That service included founding the division of clinical pharmacology at the Uniformed Services University of Health Services, a military medical school in Washington, D.C.

He was next recruited to become the director of the FDA Center for Drug Evaluation and Research, CDER, where he served for six years and was personally involved in reviewing numerous INDs and NDAs.[57] Next he went to Georgetown University as a professor of pharmacology, founding the Center for Drug Development Science and consulting with companies. He is currently consulting and is designated as a "special government employee" available to consult with the FDA. He was accepted to

[57] While serving as director of CDER, Dr. Peck was also named Assistant Surgeon General of the United States. (Dkt. 337 at 11.)

testify as an expert in scientific standards regarding determinations of the efficacy and safety of pharmaceutical drug products. (Dkt. 337 at 4–16).[58]

Dr. Peck testified with reference to the asserted limitations of the patents-in-suit claiming a formulation intended for IV administration to a human to reduce the likelihood of CINV. He stated that in his opinion, a POSA in the relevant time period would require "fully analyzed results of two adequate and well controlled Phase III studies" in order to determine that a drug formulation would be effective for reducing the likelihood of CINV. (Id. at 22.) It was further his opinion that the pharmaceutical formulations relevant to the patents-in-suit "were not known to work for their intended purpose of reducing the likelihood of CINV in human patients" before January 30, 2002. (Id. at 78.)

Dr. Peck gave three reasons for his opinions. First, the results of a single Phase III trial would not be sufficient for a POSA to know that the drug was efficacious. Second, assuming that the results of a single Phase III were sufficient, the preliminary results from such a study would provide only insufficient information. Third, under the "impossible hypothetical" that Phase III trials were not needed in this case, the Phase II 2330 study as reported "provided only a signal," and the FDA itself said it was insufficient as a pivotal trial, so that would also not be sufficient to convince a POSA of efficacy. (Id.) He added that a pharmaceutical formulation could not be used for IV administration to a human to reduce the likelihood of CINV without FDA approval, except under an active FDA-approved IND. (Id. at 24.)

[58] Teva did not object to Dr. Peck being admitted to testify as offered, but did express a relevance issue with his testimony. (Dkt. 337 at 20.)

He stated that the standards he employed were scientific standards that he thinks a POSA (as defined by plaintiffs) would embrace. He explained that "[t]hese are standards that have been developed by a consensus of scientists over many decades. Since FDA is a science-based agency and ... uses science all the time in its review and guidance and decisions," he referred to FDA standards in forming his opinions in this case. (Id. at 24.) He testified that the FDA is very highly regarded as a scientific and regulatory agency, stating, "I think scientists in the industry and scientists in the academic community recognize that those standards are their standards." (Id. at 26–27.)

Dr. Peck testified that with regard to clinical trials, the FDA sets the standards, and it provides guidance. Importantly, he said, it has "articulated a statistical framework for being able to really know from the data, particularly data that's highly variable, that a drug is working." (Id. at 26.)

Addressing Dr. Fruehauf's reliance on Phase II data in his opinion testimony, Dr. Peck commented that "Phase II studies, with a few exceptions, are never capable of permitting a POSA to really know that the drug will be effective in the broad range of patients that will be candidates for the drug if and when the drug is actually approved." (Id. at 33.) He explained the reasons included that those studies are typically small, they are often very limited in the type of patients, and they often produce confusing results. (Id. at 33–34.)

Contrasting the purpose and structure of Phase II trials with that of Phase III trials, Dr. Peck described Phase III trials as follows:

> [T]he basic standard for knowing that a drug will work, and one that you can generalize to all patients that would be candidates in the future, are the Phase III trials. These are defined as adequate and well controlled, meaning they're large. They're structured with sound statistical principles. There is a wide range of patients ... so that they are representative. And they're positioned, also, to provide a much richer collection of data that will be important to the prescriber and to the patient that can be articulated in the prescribing information, the so-called drug label.

(Id. at 34.)

He also explained the reason why two Phase III trials are generally necessary to know whether a pharmaceutical product would work for its intended purpose, which is replication. "[S]cientists always know that one experiment is not necessarily reproducible.... [T]he basic, good science requires replication. So you need at least two." (Id.) He said that 40 to 60 percent of Phase II trials that advance to Phase III do not result in approved drugs because one or more of the trials will fail. (Id.) He added that a typical Phase III program in 2003 and at present, as illustrated by the Phase III trials in this case, are done in different centers by different investigators around the world, so there is independence in the replication design. He said that a drug such as palonosetron would not qualify for a single Phase III trial to get FDA approval. (Id. at 37.)

Dr. Peck reviewed the same Phase II 2330 study documents on which Dr. Fruehauf had testified. Looking at the Final Report of that study dated July 1995, Dr. Peck testified that this was one of five Phase II studies. He said it was "an exploratory dose-ranging study.... And the purpose of this was to evaluate graded doses to evaluate the safety and to identify a possible signal of benefit." (Id. at 39–40.) He noted that it was a small

study; most of the patients were male and none had received a chemotherapeutic agent before; and "that was quite unrepresentative of any broader population." (Id.)

Looking at the data in the summary table of the 2330 Final Report, see n.55 supra, Dr. Peck did point out that in the entire table there were only two findings of statistical significance, and both of them were at the 30 mcg/kg level. He also stated that there was no "ordered dose response," because even the stated results for 3 to 90 mcg/kg were 46, 40, 50, and 46. He was asked whether that could indicate that an efficacy plateau was reached at the 3 mg/kg [0.25 mg] level, and he said that was only one hypothesis that could arise from that raw data. Indeed, he said, in the other Phase II studies that were done, the best dose was one of the others. (Id. at 40–44.)

Focusing on the difference in results between the 24% figure for the lowest .3 to 1 mcg/kg dose and the 46% result for the 3 mcg/kg dose, he said that might or might not indicate efficacy, stating, "[t]he scientific method, the agreed-upon approach in drug studies, is to couple an apparent difference with a statistically significant difference so that if you were to repeat this trial, you would get the same result.... I really can't conclude anything from the 24 versus 46 because this could change in the next study. It's too small a study." (Id. at 44–45.)

Dr. Peck also reviewed the minutes of the March 10, 1999 meeting of Helsinn with the FDA. He stated that the names of FDA representatives included the CDER division director, the medical team leader, and the medical officer (primary reviewer on the product) -- all of whom were M.D.'s, as well as two pharmacologists and a chemist. He

chaired many such meetings himself, he said, and has been to many more since leaving his CDER director position in 1993. (Id. at 52.)

He highlighted the various portions of those minutes where the FDA communicated that the Phase II 2330 study data "did not show a convincing dose-response pattern." As he characterized that discussion at the meeting:

> FDA says, well, look, first of all, there's a lack of dose response in that study, so, therefore, we really can't entertain that data set, as is, to support. However, there is a possibility -- and this is implied in the future, there is a possibility -- that the data itself may be useful as supportive data. So, this is basically a "no," that study is insufficient.

(Id. at 55.)

He also reviewed the re-analysis report of the 2330 study data that the FDA permitted Helsinn to use as support for its pivotal Phase III study PALO-99-05, PTX-182. He said it was a lengthy report that made adjustments to the data, then constructed an "historical placebo" comparator [the study itself was not designed with a placebo], and did a statistical analysis of all that data. "And with those adjustments," he said, "it turns out that the .25 milligram and the .75 ... both of them were statistically significantly different from this historical placebo, which permitted then the revised data, and analysis, to be viewed by FDA to be adequate to support the already available Phase III trial [referring to PALO-99-05, the HEC trial] that had demonstrated effectiveness." He noted the date of that re-analysis report in August 2002, well after the critical date of January 30, 2002. (Id. at 57–60 (bracketed text added).)

Addressing Helsinn's April 7, 2000 letter to the FDA submitting the November 15, 1999 proposed protocols for the three Phase III studies, Dr. Peck highlighted the contents in those documents where Helsinn said the Phase II results "suggested" efficacy, and that the Phase III trials were designed "to support the hypotheses" that palonosetron was not inferior to existing setrons. He said, "the key word here is 'hypothesis'. We don't know. If they knew, they would have filed a new drug application. They know that more studies have to be done and they're requesting permission to undertake three new ... Phase III studies." (Id. at 49.)

Dr. Peck described the three full-scale Phase III trials as all using an historical placebo control model, as well as two different comparators (ondansetron and dolasetron), and large numbers of patients at different centers. He said those were "three adequate and well-controlled Phase III clinical trials." Only the first of those three, the PALO-99-03 study, was unblinded before January 30, 2002. (Id. at 60–69.)

The sequence of events after the "last patient out" date of October 2, 2001, reflected in the Clinical Study Report for PALO-99-03, was reviewed and explained by Dr. Peck. See Section I.C.10. In response to Dr. Fruehauf's discussion of the Cantoreggi declaration and his "hypothetical" analysis of the pre-October 2, 2001 blinded data theorized by Dr. Fruehauf, Dr. Peck said he thought it would be impossible to try to guess what the efficacy outcomes were, even if the sponsor could get access to the data; nor were there any such requests reflected in the study records. (Id. at 69–70.)

Dr. Pecks's explanation of the major analytical process necessary, according to the PALO-99-03 protocols, before and after the "unblinding date" of January 2, 2002, is described above in Section I.C.10.

Referring to the Helsinn letter of February 7, 2002, transmitting to the FDA "the preliminary data for Complete Response," Dr. Peck said "the author of that letter knew exactly what he was saying. This is preliminary. This is not final. And we're just showing you a couple tables." (Id. at 76.)

Dr. Peck said that the tables attached to that February 7, 2002 Helsinn letter to the FDA were one of probably 300 tables that were under analysis at the time, and the table is expressly represented as preliminary data. He said that to evaluate the data reliably, one would need all of the supporting information and more statistical data, as was done for the final Clinical Study Report dated July 19, 2002. He said that although there is no indication that the raw data of the study was changed after the "locked" date, there was at least one amendment to the statistical analysis plan on December 13, 2001. (Id. at 165–66.)

He also did not agree with Dr. Fruehauf that there were no potential differences in the Phase II and Phase III efficacy results based on the different formulations used in those studies, referring to the saline-based solution in Phase II and the full pharmaceutical formulation in Phase III. He said the buffers differed in their constituents, and the pH was different in the two sets of studies. "So these are fundamentally different formulations," according to him. (Id. at 46.)

3. Analysis

Proof that a claimed formulation has been reduced to practice requires clear and convincing evidence that the inventor (1) constructed an embodiment that met all the limitations, and (2) determined that the invention would work for its intended purpose. Z4 Techs., Inc., 507 F.3d at 1352. Whether the formulation claimed in the patents-in-suit in this case was reduced to practice hinges on the timeline of testing and the knowledge that a person of ordinary skill would have developed in light of the historical facts. Id.

Here, the issue is whether such person would likely know that the claimed intravenous pharmaceutical formulation containing palonosetron was effective for reducing the likelihood of emesis or CINV in a human as of the critical date of January 30, 2002. The Court finds that there is not clear and convincing evidence to establish this prong of the on-sale bar test for patent invalidity. Taking in order the documents relied upon by Teva and its expert on this point, the Court makes the following factual findings. Citations to all the testimony and exhibits on these points are contained in the preceding sections of this opinion. We will use the fixed dose measure in this discussion, e.g., 0.25 mg, rather than the weight-based measure, e.g., 3 mcg/kg, shown in some of the records.

The Phase II 2330 study data, as reported in the Final Report of that study dated July 1995, showed no statistical significance in the stated primary endpoint of Complete Control for 24 hours for any dosage below 2 mg. While the 2330 study was a well-designed Phase II study for its purpose, it lacked the scope and controls that would make it a valid prediction of efficacy at any dose. The FDA so informed Helsinn at the March

10, 1999 "End of Phase II" meeting, and the Court finds that was a scientifically valid observation that a POSA would make when viewing that documentation. Syntex, which presided over all four of the completed Phase II palonosetron trials, ended its research by recommending in its Formulation Book that Phase III use a 1.0 mg dose for CINV.[59]

When Helsinn took over the palonosetron development project and assembled its project team of scientists, and advisors, they struggled long and hard to predict a possible minimum effective dose to take to Phase III trials. Even the highly respected clinician Dr. Gandara, who consulted at the week-long Helsinn Clinical Meeting in July 1998, could only posit that he thought 0.25 mg was "most likely" the correct dose for CINV. He was far superior to being an person of ordinary skill in the art, but that is how he viewed the problem at that time.

All present at that July 1999 Helsinn Clinical Meeting recognized that Phase III testing was essential to determine the efficacy and correct dosage of palonosetron in a completed pharmaceutical formulation for CINV. The fact that the outcome of that meeting in 1998 was a decision to continue to consider doses of 0.25, 0.75 and 2.0 is also a reflection of the uncertainty, in their view, of the results that might be obtained in Phase III. As Dr. Calderari also testified, even when he and Dr. Macciocchi continued debating

[59] The Court finds further verification that the Final Report of the 2330 study was not as reliable as it would need to be in the fact, not brought out in the evidence at trial, that the very table that summarized the primary endpoint data was wrong and mixed up the results of the primary and secondary endpoints -- a fact that was only discovered in the intensive re-analysis study PALO-00-01 suggested by the FDA. See n.56 supra.

the tradeoff between dosage and likely stability, Dr. Macciocchi still wanted to include a much higher dosage than 0.25 or 0.75 in Phase III.

The November 1999 proposed Phase III protocols, submitted to the FDA on April 7, 2000, made numerous statements of hopeful expectation about the 0.25 and 0.75 doses proposed for the trials. Nevertheless, the fact that Helsinn elected to test the two doses, including 0.75 mg, even though it would be a more cumbersome and expensive endeavor, reflected Helsinn's concern that it had no assurance of the efficacy at the 0.25 level. Helsinn was aware, as it stated there, that its "hypotheses" were to be tested in Phase III. Helsinn's statement in the same document that it was "clear" that 0.25 was the minimum effective dose was just one among many less confident statements in the proposal. Likewise, Helsinn's press release statement, at the start of patient enrollment for the trials, that "the Phase II trials demonstrated the efficacy" of the drug was in the nature of a marketing piece rather than any statement of scientific knowledge. Again, in context, the fact that Phase III trials were commencing meant that Helsinn had no such knowledge at that time.

This Court is also not persuaded that the "preliminary" unblinded data of the earliest Phase III study, PALO-99-03, shown in the three tables dated January 7, 2002, sent to the FDA on February 7, 2002, informed Helsinn or a POSA that the 0.25 mg dose was effective for CINV, which was the only kind of emesis that was even studied at the Phase III level. Those tables were generated a mere five days after the Phase III data was "unblinded," and less than three weeks after the data was "locked" on December 19,

2001. More than six months of additional analytical work lay ahead at that time, leading to the final Clinical Study Report dated July 19, 2002. Indeed, there had already been one amendment to the statistical design of the study on December 13, 2001, and more amendments to the analytical process were entirely possible in the months to follow.[60]

The fact that the summary tables of preliminary data dated January 7, 2002 did not undergo change in their contents during that analytical period, and that data was the same in the final Clinical Study Report as of July 19, 2002, does not in the view of the Court establish that the preliminary results were final. Quite the contrary; it would seem that in view of the changes in methodology that were entirely possible during the analytical period (as experts on both sides agreed), a POSA would not have been surprised at all to see those values change between the preliminary and the final numbers. The Helsinn press release on January 16, 2002 was consistent with that understanding, saying, "[w]e are pleased to have completed all patient treatment and to have begun analysis of the data." See n.36 supra.

The Cantoreggi declaration did state factual truth, based on the historical evidence that the declarants were reconstructing for that PTO submission. It was in an unrelated patent family history, but the Court has carefully considered its content as relevant to the "ready to patent" issue here. The factual content of that declaration states that "we had conceived the idea to use 0.25 mg. palonosetron for the treatment of acute and delayed-

[60] Another indicator of the fluidity of the analytical process during that period, although not addressed by the witnesses at trial, is seen in the section of the PALO-99-03 Clinical Study Report entitled "Additional changes after unblinding," quoted in n.38 supra.

onset CINV ... as least as early as August 1, 2001 (the date that the study [PALO-99-03] began)." "[W]e had successfully tested the method in human patients, and we had done so before October 2, 2001 (the date the study was completed)." (DTX-0287-0415 (bracketed text added).) Both of those facts were literally true. But there is no evidence in this record that Helsinn knew or could have known, until the results of the study were processed, locked, unblinded, and fully analyzed, that those results were successful, nor did the declarants so state. As for the declaration statement that the invention had been "reduced to practice" before November 16, 2001, that was not a statement of historical fact but a use of legal language to support an ultimate factual conclusion at best, and is not binding upon this Court in analyzing the factual issues here.

Teva's expert, Dr. Fruehauf, opined that the results of the Phase II 2330 study, coupled with the preliminary results of the Phase III PALO-99-03 study, were sufficient to have informed a POSA that palonosetron was effective to reduce the likelihood of CINV (which is emesis, as claimed in the first three patents-in-suit), and also that the 0.25 dose of palonosetron was effective to reduce the risk of CINV as claimed in the '219 patent. This Court does not find that the evidence supports such a finding under the clear and convincing standard of proof that applies to this determination.

It is not necessary for the Court to make a further ruling as to whether, as Dr. Peck opined, fully analyzed results of two adequate and controlled Phase III studies were necessary in this particular case to establish the efficacy of the claimed palonosetron formulation. The date when the action stopped, for purposes of the on-sale bar in this

case, was January 30, 2002. At that time there were no fully analyzed Phase III studies in this case. Further, as the Court has found, the Phase II data would have been wholly insufficient at that time to support any valid scientific knowledge of efficacy as claimed. Accordingly, for the reasons stated here, and based on all other historical facts described in Section I.C, the Court finds that the patent challenger has not shown by clear and convincing evidence that as of January 30, 2002, the inventor had determined that the invention would work for its intended purpose.

5. Conclusions as to on-sale bar claims

The Court has made the following findings and conclusions in this section, all directed to Teva's claim that the patents-in-suit are invalid under the on-sale bar provision of 35 U.S.C. § 102.

- The MGI Agreement was a "sale" under the pre-AIA. See Section II.A.2.
- The Oread and SP Agreements were not "sales or offers to sell" under the pre-AIA. See Section II.A.2.
- The MGI Agreement was not a "sale" under the AIA. See Section II.A.3.
- Defendant has not shown by clear and convincing evidence that as of January 30, 2002, the inventor had determined that the invention would work for its intended purpose. See Section II.A.4.

B. Written Description

1. Legal standards

A patent must contain "a written description of the invention." 35 U.S.C. § 112(a). "[T]he hallmark of written description is disclosure." Alcon Research Ltd. v. Barr Labs.,

745 F.3d 1180, 1190 (Fed.Cir. 2014). The disclosure must "allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described." Enzo Biochem, Inc., 323 F.3d at 968. The disclosure need not contain "either examples or an actual reduction to practice"; rather, the critical inquiry is whether the patentee has provided a description that "in a definite way identifies the claimed invention" in sufficient detail that a person of ordinary skill would understand that the inventor was in possession of it at the time of filing. Alcon Research, 745 F.3d at 1190–91. This is an objective inquiry "into the four corners of the specification." Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed.Cir. 2010). "A claim that recites a property that is necessarily inherent in a formulation that is adequately described is not invalid as lacking written description merely because the property itself is not explicitly described." Allergan v. Sandoz, Inc., 796 F.3d 1293, 1309 (Fed.Cir. 2015).

A patent is presumed valid, and this presumption can be overcome only by facts supported by clear and convincing evidence to the contrary. Enzo Biochem. Inc., 323 F.3d at 962.

2. Findings and conclusions on written description

Teva asserts that if the Court finds that fully complete Phase III data would be required as claim support in order for the '219 patent to be "ready for patenting" under the on-sale bar, then that patent is invalid for lack of written description because there is

no Phase III data, or for that matter any preclinical or clinical efficacy data, in the specification. (Dkt. 312 at 34–35.)

Helsinn argues that the '219 patent specification does satisfy the written description requirement in that it does describe the claimed inventions, both as to formula and as to efficacy. Helsinn cites the formula embodiment described in the specification, "the palonosetron is supplied in vials that comprise 5 ml. of solution, which equate to about 0.25 mg of palonosetron at a concentration of about 0.05 mg/ml." (DTX-0268, col. 10, lines 7–8; see dkt. 311 at 39.) The efficacy information described in the specification is further cited on this point:

> Recently, clinical investigations have been made concerning palonosetron, a new 5-HT3 receptor antagonist reported in U.S. Pat. No. 5,202,333. These investigations have shown that the drug is an order of magnitude more potent than most existing 5-HT3 receptor antagonists, has a surprising half-life of about 40 hours, and is effective to reduce delayed-onset nausea induced by chemotherapeutic agents.

(DTX-0268, col. 1, lines 43–54; see dkt. 311 at 39–40.)

A second point emphasized by Helsinn is that the on-sale bar "ready for patenting" prong is measured on the date one year prior to the patent application filing date, whereas written description information includes that intervening year and what a POSA would know from publicly available data as of the application date. (Dkt. 320 at 102.) Here, it is undisputed that between January 30, 2002 and January 30, 2003, there was at least one public disclosure of details about the clinical efficacy of the 0.25 mg dose. The PALO-99-04 study results were summarized, in an abstract presented by Helsinn's Dr.

Macciocchi and researchers who worked on that trial, at a conference of the Multinational Association of Supportive Care in Cancer ("MASCC") on June 23–26, 2002 in Boston. (PTX-297.) See Section I.C.11.[61] Teva's expert Dr. Fruehauf agreed that the data shown in that Grunberg abstract supports the stated conclusion of the authors. (Dkt. 324 at 124–29.)

Finally, Helsinn argues that the Allergan decision "slammed the door" on the written description defense as asserted here, as the Federal Circuit held that a claim that recites a property that is necessarily inherent in the formulation is not invalid for lack of written description, even if such property is not "explicitly described." (Dkt. 353 at 152.)

The Court finds that the specification of the '219 patent provides an adequate written description of the efficacy of the invention claimed. See 35 U.S.C. § 112(a). The specification discloses the claimed formulations, and the Court finds that as of the provisional application date of January 30, 2003, a skilled artisan "would immediately discern the claimed formulation in that disclosure." Moreover, actual data from the PALO-99-04 Clinical Study was publicized by Helsinn at the MASCC conference in June 2002. The Court is also persuaded by Allergan, which held that a property inherent to a claimed formulation is not lacking a written description merely because the property is

[61] The parties also agree that the published prior art in this case is defined under 35 U.S.C. §102(b), so the operative date for published prior art relevant to obviousness is January 30, 2002, which is one year before the priority date of January 30, 2003. (Dkt. 328 at 240–41.) This published reference in June 2002 would not therefore qualify as §102(b) prior art, but is relevant to what a POSA would know, for purposes of written description analysis, on January 30, 2003.

not "explicitly described" in the specification. Id. Rather, the critical inquiry is whether the formulation itself is adequately described. See id.

Here, the Court is satisfied that Helsinn's claim for a palonosetron formulation "to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting" is adequately supported by the written description in the specification. The Court finds that this description, especially in view of the June 2002 public disclosure, is adequate such that a skilled artisan would have knowledge that the inventors were in possession of the invention at the time of the patent application, and that there is no clear and convincing evidence to the contrary.

C. Infringement

1. Legal standards

Section 271(e)(2)(A) of the Patent Act provides that:

> It shall be an act of infringement to submit--(A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent . . . .

35 U.S.C. § 271(e)(2)(A).

Under the Hatch–Waxman framework, the filing of an ANDA constitutes an artificial act of infringement for purposes of creating case or controversy jurisdiction. Ferring B.V. v. Watson Labs., Inc.-Fl., 764 F.3d 1401, 1408 (Fed.Cir. 2014) ("Ferring II"); see also Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 676 (1990). This artificial, or technical, act of infringement does not in and of itself constitute a literal infringement. See Ferring II, 764 F.3d at 1408 ("The district court here thus erred to the extent that it read § 271(e) to mean that [defendant's] act of filing an ANDA, by itself, established infringement . . . ."). Indeed, once

jurisdiction has been established by way of § 271(e)(2)'s technical act of infringement, "traditional patent law principles" control and a court must conduct a traditional infringement analysis. See id. This analysis requires a "comparison of the asserted patent claims against the product that is likely to be sold following ANDA approval . . . ." See id. Moreover, it requires the patentholder to prove the infringement of the asserted patent claims by a preponderance of the evidence. See Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1567 (Fed.Cir. 1997) ("The plain language of the statute does not alter a patentee's burden of proving infringement, nor does it mandate an infringement analysis limited to the scope of the approval sought."). As will be discussed below, a court's analysis differs based upon whether the ANDA specification directly resolves the infringement question or is silent as to the infringement of asserted patent claims.

"[I]f a product that an ANDA applicant is asking the FDA to approve for sale falls within the scope of an issued patent, a judgment of infringement must necessarily ensue." Sunovion Pharms., Inc. v Teva Pharms., USA, Inc., 731 F.3d 1271, 1278 (Fed.Cir. 2013). In Sunovion, the ANDA applicant requested approval of an amount of stereoisomer ranging from 0.0 to 0.6%. See id. at 1274–75. The patentholder argued that the ANDA specifications infringed its patent, which claimed a stereoisomer of "less than 0.25%." See id. at 1274. The Federal Circuit noted that while the filing of an ANDA itself "constitutes a technical infringement for jurisdictional purposes," a traditional infringement analysis is required to determine whether a court should enter a judgment of infringement. See id. at 1278. The Sunovion court looked to the ANDA specifications, as this was the "subject matter that

determines whether infringement will occur." See id. The court held that the ANDA applicant's request for approval for an isomer amount of 0.0 to 0.6% fell squarely within the scope of the "less than 0.25%" limitation set forth in the asserted patent claims and entered a judgment of infringement. See id.

Conversely, "[i]f any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." See Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1247 (Fed.Cir. 2000). The asserted patent claims at issue in Bayer involved a pharmaceutical composition with a specific surface area ("SSA") of 1.0 to 4m^2/g. See id. at 1246. The ANDA applicant requested approval from the FDA of a bioequivalent product with a SSA of 5m^2/g or greater. See id.[62] The court noted that "[t]he focus under § 271(e)(2)(A), is on what the ANDA applicant will likely market if its application is approved, an act that has not yet occurred." See id. at 1248 (quotation and citation omitted). "[T]his hypothetical inquiry is properly grounded in the ANDA application and the extensive materials typically submitted in its support." See id. However, if the ANDA applicant requests approval of a "well-defined compound, then the ultimate question of infringement is usually straightforward." Id. at 1249. The Federal Circuit reasoned that because the applicant's ANDA specification included a compound which "cannot have a SSA of less than 5m^2/g . . . [the applicant] cannot literally infringe the '446 patent." See id.

[62] The district court had also noted that the ANDA applicant's supplier did not sell the composition with a SSA under 4.7m^2/g in the United States. See Bayer, 212 F.3d at 1246.

"In cases in which the ANDA specification does not resolve the infringement question in the first instance, [the Federal Circuit has] endorsed the district court's reference to relevant evidence, including biobatch data and actual samples of the proposed generic composition that the ANDA filer had submitted to the FDA." Ferring II, 764 F.3d at 1409 (citing Glaxo, 110 F.3d at 1567); see also Ferring B.V. v. Watson Labs., Inc.-Fl., 764 F.3d 1382, 1387–88 (Fed.Cir. 2014) ("Ferring I") ("When an ANDA is silent with respect to infringement . . . the correct analysis is under Glaxo . . . , not Sunovion.").

In Glaxo, an ANDA applicant filed for approval of a crystalline compound ("Form 1"). See Glaxo, 110 F.3d at 1564. The ANDA also specified that "the marketed product [would] be approximately 99% pure Form 1 [of the compound]." See id. The patentholder for a different crystalline form ("Form 2") brought suit under § 271(e)(2), alleging that the ANDA applicant infringed its Form 2 patent claim. See id. The ANDA application did not explicitly address what amount of Form 2, if any, would be present in the approved product. See id. at 1566 (internal quotation omitted) ("The [district] court also found that the . . . evidence before it demonstrated in clear and convincing fashion that Novopharm's product would not contain any Form 2 RHCl and thus would not infringe . . . [the patents].").

The court acknowledged that because the "crystalline compound was capable of existing in multiple crystalline forms, or mixtures thereof, the ultimate question of infringement is not so simple." See id. at 1569. In its analysis, the court reiterated that "the statute [§ 271(e)(2)(A)] requires an infringement inquiry focused on what is likely to be sold following FDA approval."

Id. at 1568. When the ANDA specifications do not directly resolve this inquiry, then all relevant evidence, including materials that the applicant submitted to the FDA, as well as the ANDA itself, should be considered by the court. See id. at 1568–70. The court noted that these materials include "actual samples" and "extensive technical data required by the FDA." See id. at 1569 n.2. The Federal Circuit affirmed the district court's finding that the patentholder had failed to prove infringement by a preponderance of the evidence and noted that the court "properly considered the ANDA itself, the materials submitted by Novopharm to the FDA, and other pertinent evidence provided by the parties." See id. at 1570.

2. Findings and conclusions on infringement

a. Parties' arguments

Plaintiffs argue that there is "no genuine dispute that the CINV dosage strength in Defendants' respective ANDAs literally meets all of the limitations of the asserted claims of the '219 patent." (Dkt. 207 at 12.) Plaintiffs assert specifically that: (1) this Court should interpret § 271(e)(2)(A) as a substantive infringement test for Hatch-Waxman cases, as well as a jurisdiction-conferring statute; (2) their position on ANDA infringement is supported by current Federal Circuit precedent; (3) Teva fails to cite any authority in support of its non-infringement position; and (4) Teva's characterization of the different dosage strengths as different products is inapposite to the infringement inquiry under § 271(e)(2)(A). (See, e.g., dkt. 207; dkt. 225; dkt. 237; dkt. 353 at 89–90.)

Plaintiffs argue as a threshold matter that § 271(e)(2)(A) is more than a "subject matter conferring statute" and should be interpreted as "the substantive test for infringement in these Hatch-Waxman Act cases." (Dkt. 353 at 90.) Plaintiffs assert that under AstraZeneca v. Apotex, 669 F.3d 1370 (Fed.Cir. 2012), the Federal Circuit held that § 271(e)(2)(A) "establishe[s] a specialized new cause of action for patent infringement." (Dkt. 207 at 12 (quotation and citation omitted).) This new cause of action "directs our analysis to the scope of approval sought in the ANDA." (Id. (quotation and citation omitted).) Plaintiffs argue that under AstraZeneca, "seemingly there should be no dispute here" because Teva has filed an ANDA requesting approval to sell a product in the CINV dosage strength. (Dkt. 353 at 90; see also dkt. 207 at 13–14.)

Plaintiffs next assert that their position is supported by current Federal Circuit precedent. (See dkt. 237 at 5.) Plaintiffs analogize this case to Sunovion, asserting that Teva's ANDA for the CINV dosage strength alone "satisfies the limitations of the asserted claims . . . regardless of whether approval is also sought for other dosage strengths of that product." (See dkt. 207 at 13.) Plaintiffs note that the Federal Circuit found that the ANDA applicant in Sunovion had infringed even though the applicant requested approval for isomers that fell outside of the "less than 0.25%" asserted patent claim (i.e., 0.26% to 0.6%.) (See id.) Plaintiffs state that "[t]his is analogous to the two dose/volume values that are possible based upon the amount of otherwise identical 0.05 mg/mL palonosetron solution poured into the vials for each dosage strength." (Dkt. 237 at 6.) Plaintiffs distinguish this case from the Glaxo/Ferring line of cases, wherein the ANDA is silent as to the issue of infringement, and note that "if Defendants' approach were

correct, then [the ANDA applicant in Sunovion] would have been permitted to sell the 0.3–0.6% isomers . . . ." (See dkt. 225 at 9.)

Plaintiffs also argue that Teva has failed to cite to any authority in support of a finding of non-infringement of the '219 patent. (See dkt. 237 at 10.) Plaintiffs assert that Teva's citation of Ferring I and Ferring II as support for the application of a Glaxo analysis (i.e., looking to the product likely to be sold following ANDA approval) in this case, is misplaced. (See id. at 7–8.) Plaintiffs note that Ferring I and Ferring II clarified that the ANDA specification is central to any infringement analysis, and that a Glaxo analysis applies only when an ANDA is silent as to the asserted patent claims. (See id.)

Plaintiffs further argue that Teva's characterization of the CINV dosage strength and PONV dosage strength as different products is "immaterial, as it cannot be disputed that each of Defendants' ANDAs contains only one ANDA specification defining the scope of approval sought from the FDA." (Dkt. 225 at 5.)[63] Plaintiffs also note that Teva "do[es] not even address the fact that they can remove the CINV dosage strength from their respective ANDAs, if desired." (See dkt. 237 at 9.)

Teva argues that (1) its PONV dosage strength does not meet "each and every limitation of the asserted claims;" and (2) that Plaintiffs have failed to show by a

[63] Plaintiffs asserted in their opposition memorandum that Teva amended its ANDA to remove the PONV dosage strength "i.e., the entire basis for its summary judgment motion." (See dkt. 225 at 6.) Teva, in reply, denies amending its ANDA to remove the PONV dosage strength. (See dkt. 234 at 5–6.) Teva states that it has "always sought, and continues to seek, final marketing approval from the FDA for this product." (Id. at 6.) The Court will not address this argument as Teva has maintained that it did not amend its ANDA.

preponderance of the evidence that Teva's PONV dosage strength product infringes the '219 patent. (See dkt. 202 at 11; dkt. 234 at 7–8.)

Teva first argues that its PONV dosage strength does not meet "each and every limitation of the asserted claims." (Dkt. 202 at 11.) Plaintiffs' asserted patent claims "require a formulation that includes palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base." (Id. at 12 (quotation omitted).) Teva notes that its PONV dosage strength includes a total drug content of only 0.075 mg of palonosetron hydrochloride based on the weight of its free base. (See id.) Teva asserts that "[a]s a matter of law, 0.075 mg cannot be equivalent to 0.25 mg." (Id. (citation omitted).) Moreover, Teva points out that the asserted patent claims require a formulation that has a 5 ml sterile aqueous isotonic solution, whereas Teva's 0.075 mg/1.5 ml product has a solution volume of only 1.5 ml. (See id.) Lastly, Teva notes that Plaintiffs' intended use language is "to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting." (Id. at 13.) Teva argues that its PONV dosage strength product is labeled for the treatment of postoperative nausea and vomiting, and "thus cannot be equivalent." (See id.)

Teva asserts that Plaintiffs have failed to prove, by a preponderance of the evidence, that the PONV dosage strength product infringes the asserted claims under the '219 patent. (See dkt. 234 at 7–9.) Teva argues that Plaintiffs misconstrued the holding in Sunovion, noting that "the Sunovion court used the ANDA specification to define the

product on which to base the infringement inquiry." (Id. at 8.) Teva emphasizes that its ANDA specification defines the product—0.075 mg/1.5 ml—and that "there is no question that the 0.075 mg/1.5 ml product, as described in Teva's ANDA, does not meet the limitations of the '219 patent." (See id. at 9.)

Teva further distinguishes AstraZeneca by noting that regardless of whether the Federal Circuit established a substantive test for infringement under § 271(e)(2)(A), the court nevertheless held that the patentholder failed to establish, by a preponderance of the evidence, that the ANDA applicant had infringed the asserted patent claims. (See dkt. 221 at 12.) Teva noted that AstraZeneca did not change the Federal Circuit's holding in Glaxo that § 271(e)(2) "does not alter a patentee's burden of proving infringement." (See id. (citing Glaxo, 110 F.3d at 1567).)

b. Analysis

The Court, having considered the parties' arguments, finds that Plaintiffs have not established by a preponderance of the evidence that Teva's 0.075 mg/1.5 ml product infringes the asserted claims of the '219 patent under § 271(e)(2)(A).

Plaintiffs argue as a threshold matter that § 271(e)(2)(A) not only establishes subject matter jurisdiction, but also sets forth the substantive test for infringement under Hatch-Waxman Act litigation. (See dkt. 353 at 89–90; see also dkt. 207 at 13.) Plaintiffs state that the Federal Circuit followed this very approach in AstraZeneca, in which the court held that § 271(e)(2)(A) "establishe[s] a specialized new cause of action for patent infringement." (See

dkt. 207 at 12 (quotation and citation omitted).) In that case, the Federal Circuit agreed with AstraZeneca's jurisdictional interpretation of § 271(e)(2), but specifically held that "[w]hile the district court erroneously concluded that it lacked subject matter jurisdiction over AstraZeneca's claims, its judgment of dismissal was nevertheless correct, for we agree with the district court's underlying determination that AstraZeneca failed to state a viable claim for relief under § 271(e)(2)." AstraZeneca, 669 F.3d at 1377.

The Court finds that the holding in AstraZeneca does not overrule the Glaxo holding, i.e., that the infringement inquiry under § 271(e)(2)(A) "is the same as it is in any other infringement suit, viz., whether the patent in question is invalid or will not be infringed by the manufacture, use, or sale of the drug for which the [ANDA] is submitted." Glaxo, 110 F.3d at 1569 (quotation and citation omitted). Moreover, the burden to prove infringement remains squarely on the patentholder. See id. at 1567.

These principles are not limited to those Glaxo-like cases where the ANDA specifications do not resolve the infringement question. Rather, the Federal Circuit has applied this § 271(e)(2)(A) traditional infringement analysis regardless of whether the ANDA specification resolves the infringement inquiry. See, e.g., Ferring II, 764 F.3d at 1408 ("As we have explained, once jurisdiction is established, the ultimate infringement inquiry provoked by [an ANDA] filing is focused on a comparison of the asserted patent claims against the product that is likely to be sold . . . ."); Bayer, 212 F.3d at 1249 ("[T]he focus of the infringement inquiry under . . . § 271(e)(2)(A) is on the product that will be sold after the FDA's approval of

the ANDA . . . ."). This Court will thus analyze Plaintiffs' § 271(e)(2)(A) infringement allegations under a traditional infringement analysis.

Here, Teva concedes that its 0.25 mg/5 ml CINV dosage strength product meets the limitations of the asserted claims of the '219 patent. (See dkt. 234 at 9.) However, this does not end the infringement inquiry. (See dkt. 353 at 90.) The Federal Circuit has instructed that the inquiry must focus on "a comparison of the asserted patent claims against the product that is likely to be sold." See, e.g., Ferring II, 764 F.3d at 1408. As Teva has already conceded that its CINV dosage strength product infringes the '219 patent, and leaving aside for the moment the parties' invalidity issues as to all four patents-in-suit, the only product that Teva is likely to sell is the PONV dosage strength. (See dkt. 234 at 9.) Thus, Plaintiffs must prove by a preponderance of the evidence that the PONV dosage strength product infringes the asserted '219 patent claims. See Glaxo, 110 F.3d at 1567.

Plaintiffs argue that there is "no genuine dispute that the CINV dosage strength in Defendants' respective ANDAs literally meets all of the limitations of the asserted claims of the '219 patent." (Dkt. 207 at 12.) While Plaintiffs analogize this case to Sunovion in that both applicants' ANDAs specify an infringing product, this case differs in that "Teva's ANDA specification also defines another product—the 0.075 mg/1.5 mL product." (See dkt. 234 at 9.) See also Sunovion, 731 F.3d at 1279 (quotation and citation omitted) ("[A]n ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry."). Regardless of whether Teva conceded

that one of its two proposed generic drugs infringed the '219 patent, the burden remains with Plaintiffs to prove that the remaining product in Teva's ANDA specification—the PONV dosage strength product—infringed the '219 patent by a preponderance of the evidence. Plaintiffs have failed to do so.

The Court, for the reasons stated above, finds that Teva's PONV dosage strength product (i.e., its 0.075 mg / 1.5 ml product) does not infringe the asserted claims of the '219 patent.

D. Defining the Person of Ordinary Skill in the Art

The obviousness analysis is conducted from the perspective of a person of ordinary skill in the prior art ("POSA"). 35 U.S.C. § 103(a). The same POSA features in the legal standards for the "ready to patent" prong of the on-sale bar under 35 U.S.C. § 102(a), and for written description under 35 U.S.C. § 112. See Sections II.A.4 and II.B.1. The Court is defining POSA here as it relates to the entire patent dispute.

The hypothetical person of ordinary skill "is presumed to be aware of all the pertinent art" at the time the invention was made. AstraZeneca Pharms. LP v. Anchen Pharms., Inc., Nos. 10-1835, 10-4203, 10-4205, 10-4921, 10-5519, 11-2483, 11-2484 (consolidated), 2012 WL 1065458, at *19 (D.N.J. Mar. 29, 2012) (citation omitted). The person of ordinary skill "is also a person of ordinary creativity, not an automaton." KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007).

The POSA may be a composite of various types of individuals. See AstraZeneca Pharms., 2012 WL 1065458, at *19. At issue in AstraZeneca was the validity of a patent covering: (1) sustained release formulations of quetiapine, a compound useful as an antipsychotic agent; and (2) treatment methods that included "[a] method of treating psychotic states or hyperactivity in a warm-blooded animal which comprises administering to said … animal an effective amount of a formulation of [any one] of [the] claims." Id. at *20–21. The AstraZeneca court defined the person of ordinary skill as a "clinician or an antipsychotic drug researcher," and a "formulation scientist." See id. at *21–22. Each composite of the POSA took into account the educational level of the inventor and an active worker in the field, as well as the types of problems and solutions encountered in the art, the rapidity of innovation, and sophistication of the technology. See id. at *19.

1. Expert testimony

Plaintiffs' expert Dr. Gordon Amidon testified at trial that he would define a POSA as an individual comprising the various facets of a "drug development team" including a pharmaceutical scientist, clinician, and formulation scientist. (See dkt. 342 at 147–48, 152 (sealed).) Dr. Amidon explained that a POSA composed of different fields was necessary because of the interdisciplinary nature of drug development. (See id. at 152.) He explained that a pharmaceutical scientist is necessary for the "physical chemistry and preformulation science" involved in drug development. (Id. at 153.) A clinician is required to establish "clinical parameters," i.e., the dose and the efficacy of the drug. (Id. at 157.) Dr. Amidon also testified

that while a formulation scientist would be involved throughout the entire drug development process, it is the formulation scientist's expertise that ensures a stable product and addresses any manufacturing issues that may arise towards the end of a drug development project. (Id. at 158–59.)

Dr. Amidon's testimony also touched upon the educational qualifications of a POSA. (See dkt. 342 at 148.) He testified that a POSA would have a degree in a chemistry-related field ("pharmaceutical chemistry," "pharmacy," medicine," "clinical pharmacology," or "general pharmaceutical science") with a B.S., M.S., Ph.D., or M.D. The POSA, by way of incorporating the skill set of a pharmaceutical scientist, would have a knowledge of statistics as well. (See dkt. 342 at 147–48.)

Teva's expert, Dr. Lee Kirsch, proposed a hypothetical POSA as "a formulation scientist typically with a Ph.D. in pharmaceutics or a related field and would have a couple of years of experience in developing I.V. formulations." (Dkt. 326 at 19.) Dr. Kirsch also testified that a POSA would "collaborate with others of ordinary skill in the art" and would "draw upon the knowledge and expertise of clinicians and pharmacologists . . . ." (Id. at 20.)

2. Analysis

The parties do not seem to dispute that a POSA would have an advanced degree in a chemistry-related field, or alternatively, a bachelor's degree with a greater number of years of relevant experience. (Compare dkt. 342 at 148 (requiring "two, three, four years" of relevant experience "depending on the level of education"), with dkt. 326 at 19 (testifying that POSA

would typically possess a Ph.D. in pharmaceutics or a related field and have "a couple of years of experience" in developing I.V. formulations).) The parties also do not dispute that the POSA would include a formulation scientist. (See dkt. 326 at 19; dkt. 342 at 152.)

However, the parties disagree about whether the POSA also should include the knowledge and skills of a clinician or a pharmaceutical scientist, or whether it suffices that the formulation scientist "collaborates" with these individuals. (See id.) Helsinn contends that the POSA would take into account the interdisciplinary nature of drug development and would include both a clinician and pharmaceutical scientist into the POSA definition; Teva argues that the POSA is limited to the formulation scientist. (See id.)

We find merit in Plaintiffs' contention that the person of ordinary skill in the art would possess all the attributes of a multi-member drug development team. The '219 patent is not limited to formulation, but rather includes treatment-like methods as the Court has construed it. (See DTX-0268, col. 10, lines 1–38; dkt. 290.) The parties have stipulated to a similar construction of the claim preambles of the '724, '725, and '424 patents. (Dkt. 290 at 12.) Thus, the "pertinent art" of these patents includes the field of pharmaceutical science, i.e., selecting the API and using the physical chemistry of the API to match it to a delivery system, formulation, or dosage form; the field of clinical medicine, i.e., establishing the dosing, volume, safety, and efficacy of the drug product; and the field of formulation pharmaceuticals, i.e., creating stable formulations of the active pharmaceutical ingredient in preparation for manufacturing. (See dkt. 342 at 134–36, 152–59.)

Dr. Amidon's testimony on defining the POSA encompasses this entire drug development process and his hypothetical POSA included the various professionals and skill sets that are required during this process. (See id.) Conversely, Dr. Kirsch's hypothetical POSA did not consider crucial parts of the drug development process, such as selecting an API or dosage forms. (See dkt. 353 at 128.) As Helsinn argued at trial, Teva's POSA analysis runs afoul of Insite, wherein the Federal Circuit cautioned against an "overly narrow statement of the problem," as this can become a "prohibited reliance on hindsight." Insite Vision Inc. v. Sandoz, Inc., 783 F.3d 853, 859 (Fed.Cir. 2015). (See also dkt. 353 at 128.) Here, Dr. Kirsch's hypothetical POSA "is assigned a particular formulation problem" with issues such as "choosing active ingredients or dosage forms" already decided. (See id. at 128.)

Accordingly, the Court finds that a person of ordinary skill in the art pertinent to the '219 patent would include a pharmaceutical scientist, clinician, and formulation scientist. The pharmaceutical scientist and formulation scientist would have two to four years of relevant experience in their field, as well as an advanced degree in a chemistry-related field, discussed supra. The clinician would have experience in "the therapeutic area" that is the focus of the API, or in this case, treating humans affected by cancer chemotherapy-induced nausea and vomiting. (See dkt. 342 at 134.)

CONCLUSION

This Supplemental Opinion constitutes the Court's further findings of fact and conclusions of law, pursuant to Federal Rule of Civil Procedure 52(a), on the issues addressed

in this opinion. This Supplemental Opinion supersedes the Memorandum Opinion filed here on November 13, 2015 (dkt. 360) only as to the rulings set forth herein. All other rulings set forth in the Memorandum Opinion filed on November 13, 2015 remain in full force and effect.

Based upon the evidence and the findings in this Supplemental Opinion, the Court concludes, under the standard of proof applicable on each of the following issues, that:

(1) Teva proved that the MGI Agreement was a "sale" under pre-AIA;

(2) Teva did not prove that the Oread and SP Agreements were "sales or offers for sale" under pre-AIA;

(3) Teva did not prove that the MGI Agreement was a "sale" under the AIA;

(4) Teva did not prove that the claimed invention of the asserted claims of the '724, '725, '424, or '219 patent was "ready for patenting" as of January 30, 2002;

(5) Therefore, Teva did not prove that the '724, '725 and '424 patents are invalid under the pre-AIA on-sale bar;

(6) Teva did not prove that the '219 patent is invalid under the post-AIA on-sale bar;

(7) Teva did not prove that the specification of the '219 patent fails to provide adequate written description under 35 U.S.C. § 112(a);

(8) Assuming that the '724, '725, and '424 patents are valid, as the Court has found, the Court agrees with the parties' stipulation that both the 0.075 mg dose and the 0.25 mg dose generic product specified in Teva's ANDA will infringe those three patents;

(9) Assuming that the '219 patent is valid, as the Court has found, the Court agrees with the parties' stipulation that the 0.25 mg dose generic product specified in Teva's ANDA will infringe the '219 patent; and

(10) Assuming that the '219 patent is valid, as the Court has found, the Court further finds that plaintiffs did not prove that the 0.075 mg dose generic product specified in Teva's ANDA will infringe the '219 patent.

This unsealed Supplemental Opinion supersedes the sealed version filed on February 29, 2016 (dkt. 378), which has been vacated by an order filed on this date.

s/ Mary L. Cooper
MARY L. COOPER
United States District Judge

Dated: March 3, 2016